

48



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A01N 37/28		A1	(11) International Publication Number: WO 98/38859
			(43) International Publication Date: 11 September 1998 (11.09.98)
(21) International Application Number: PCT/US98/04300		(74) Agents: GAMSON, Edward, P. et al.; Welsh & Katz, Ltd., 22nd floor, 120 South Riverside Plaza, Chicago, IL 60606 (US).	
(22) International Filing Date: 4 March 1998 (04.03.98)			
(30) Priority Data: 60/035,182 4 March 1997 (04.03.97) US		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GH, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): MONSANTO COMPANY [US/US]; 800 North Lindbergh Boulevard #04E, St. Louis, MO 63167 (US).			
(72) Inventors; and (75) Inventors/Applicants (for US only): McDONALD, Joseph, J. [US/US]; 1036 Johanna Drive, Ballwin, MO 63021 (US). BARTA, Thomas, E. [US/US]; Apartment #3W, 1133 Maple Avenue, Evanston, IL 60202 (US). BECKER, Daniel, P. [US/US]; 1427 Pebble Creek Drive, Glenview, IL 60025 (US). BEDELL, Louis, J. [US/US]; 1832 E. Camp McDonald Road, Mt. Prospect, IL 60056 (US). RAO, Shashidhar, N. [US/US]; 43 Windsor Place, Mundeleine, IL 60060 (US). FRESKOS, John, N. [US/US]; 7572 York, Clayton, MO 63105 (US). MISCHKE, Brent, V. [US/US]; 25 White River Lane, Defiance, MO 63341 (US).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(54) Title: SULFONYL DIVALENT ARYL OR HETEROARYL HYDROXAMIC ACID COMPOUNDS			
(57) Abstract A sulfonyl divalent aromatic or heteroaromatic ring hydroxamic acid compound that <i>inter alia</i> inhibits matrix metalloprotease activity is disclosed as is a treatment process that comprises administering a contemplated sulfonyl divalent aromatic or heteroaromatic ring hydroxamic acid compound in an MMP enzyme-inhibiting effective amount to a host having a condition associated with pathological matrix metalloprotease activity.			

FW 311408187 US

Atty. Docket No. 00988/1/US
Serial No. 10/618,288
Thomas E. Barta, et al.
Reference 48

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Larvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

SULFONYL DIVALENT ARYL OR HETEROARYL
HYDROXAMIC ACID COMPOUNDS

Description

5 Technical Field

This invention is directed to proteinase .
(protease) inhibitors, and more particularly to
sulfonyl divalent aryl or heteroaryl hydroxamic acid
compounds that, *inter alia*, inhibit the activity of
10 matrix metalloproteinases, compositions of those
inhibitors, intermediates for the syntheses of those
compounds, processes for the preparation of the
compounds and processes for treating pathological
conditions associated with pathological matrix
15 metalloproteinase activity.

Background of the Invention

Connective tissue, extracellular matrix
constituents and basement membranes are required
20 components of all mammals. These components are the
biological materials that provide rigidity,
differentiation, attachments and, in some cases,
elasticity to biological systems including human
beings and other mammals. Connective tissues
25 components include, for example, collagen, elastin,
proteoglycans, fibronectin and laminin. These
biochemicals makeup, or are components of structures,
such as skin, bone, teeth, tendon, cartilage,
basement membrane, blood vessels, cornea and vitreous
30 humor.

Under normal conditions, connective tissue
turnover and/or repair processes are controlled and
in equilibrium. The loss of this balance for

whatever reason leads to a number of disease states. Inhibition of the enzymes responsible loss of equilibrium provides a control mechanism for this tissue decomposition and, therefore, a treatment for these diseases.

Degradation of connective tissue or connective tissue components is carried out by the action of proteinase enzymes released from resident tissue cells and/or invading inflammatory or tumor cells. A major class of enzymes involved in this function are the zinc metalloproteinases (metalloproteases, or MMPs).

The metalloprotease enzymes are divided into classes with some members having several different names in common use. Examples are: collagenase I (MMP-1, fibroblast collagenase; EC 3.4.24.3); collagenase II (MMP-8, neutrophil collagenase; EC 3.4.24.34), collagenase III (MMP-13), stromelysin 1 (MMP-3; EC 3.4.24.17), stromelysin 2 (MMP-10; EC 3.4.24.22), proteoglycanase, matrilysin (MMP-7), gelatinase A (MMP-2, 72kDa gelatinase, basement membrane collagenase; EC 3.4.24.24), gelatinase B (MMP-9, 92kDa gelatinase; EC 3.4.24.35), stromelysin 3 (MMP-11), metalloelastase (MMP-12, HME, human macrophage elastase) and membrane MMP (MMP-14). MMP is an abbreviation or acronym representing the term Matrix Metalloprotease with the attached numerals providing differentiation between specific members of the MMP group.

The uncontrolled breakdown of connective tissue by metalloproteases is a feature of many pathological conditions. Examples include rheumatoid arthritis, osteoarthritis, septic arthritis; corneal,

epidermal or gastric ulceration; tumor metastasis, invasion or angiogenesis; periodontal disease; proteinuria; Alzheimer's Disease; coronary thrombosis and bone disease. Defective injury repair processes
5 can also occur. This can produce improper wound healing leading to weak repairs, adhesions and scarring. These latter defects can lead to disfigurement and/or permanent disabilities as with post-surgical adhesions.

10 Matrix metalloproteases are also involved in the biosynthesis of tumor necrosis factor (TNF) and inhibition of the production or action of TNF and related compounds is an important clinical disease treatment mechanism. TNF- α , for example, is a
15 cytokine that at present is thought to be produced initially as a 28 kD cell-associated molecule. It is released as an active, 17 kD form that can mediate a large number of deleterious effects *in vitro* and *in vivo*. For example, TNF can cause and/or contribute
20 to the effects of inflammation, rheumatoid arthritis, autoimmune disease, multiple sclerosis, graft rejection, fibrotic disease, cancer, infectious diseases, malaria, mycobacterial infection, meningitis, fever, psoriasis,
25 cardiovascular/pulmonary effects such as post-ischemic reperfusion injury, congestive heart failure, hemorrhage, coagulation, hyperoxic alveolar injury, radiation damage and acute phase responses like those seen with infections and sepsis and during
30 shock such as septic shock and hemodynamic shock. Chronic release of active TNF can cause cachexia and anorexia. TNF can be lethal.

TNF- α convertase is a metalloproteinase involved in the formation of active TNF- α .

Inhibition of TNF- α convertase inhibits production of active TNF- α . Compounds that inhibit both MMPs
5 activity have been disclosed in WIPO International Publication Nos. WO 94/24140, WO 94/02466 and WO 97/20824. There remains a need for effective MMP and TNF- α convertase inhibiting agents. Compounds that inhibit MMPs such as collagenase, stromelysin and
10 gelatinase have been shown to inhibit the release of TNF (Gearing et al. *Nature* 376, 555-557 (1994), McGeehan et al., *Nature* 376, 558-561 (1994)).

MMPs are involved in other biochemical processes in mammals as well. Included is the
15 control of ovulation, post-partum uterine involution, possibly implantation, cleavage of APP (β -Amyloid Precursor Protein) to the amyloid plaque and inactivation of α_1 -protease inhibitor (α_1 -PI). Inhibition of these metalloproteases permits the
20 control of fertility and the treatment or prevention of Alzheimers Disease. In addition, increasing and maintaining the levels of an endogenous or administered serine protease inhibitor drug or biochemical such as α_1 -PI supports the treatment and
25 prevention of diseases such as emphysema, pulmonary diseases, inflammatory diseases and diseases of aging such as loss of skin or organ stretch and resiliency.

Inhibition of selected MMPs can also be desirable in other instances. Treatment of cancer
30 and/or inhibition of metastasis and/or inhibition of angiogenesis are examples of approaches to the treatment of diseases wherein the selective

inhibition of stromelysin (MMP-3), gelatinase (MMP-2), gelatinase B (MMP-9) or collagenase III (MMP-13) are the relatively most important enzyme or enzymes to inhibit especially when compared with collagenase I (MMP-1). A drug that does not inhibit collagenase I can have a superior therapeutic profile. Osteoarthritis, another prevalent disease wherein it is believed that cartilage degradation in inflamed joints is at least partially caused by MMP-13 released from cells such as stimulated chondrocytes, may be best treated by administration of drugs one of whose modes of action is inhibition of MMP-13. See, for example, Mitchell et al., *J. Clin. Invest.*, 97:761-768 (1996) and Reboul et al., *J. Clin. Invest.*, 97:2011-2019 (1996).

Inhibitors of metalloproteases are known. Examples include natural biochemicals such as tissue inhibitor of metalloproteinase (TIMP), α_2 -macroglobulin and their analogs or derivatives. These are high molecular weight protein molecules that form inactive complexes with metalloproteases. A number of smaller peptide-like compounds that inhibit metalloproteases have been described. Mercaptoamide peptidyl derivatives have shown ACE inhibition *in vitro* and *in vivo*. Angiotensin converting enzyme (ACE) aids in the production of angiotensin II, a potent pressor substance in mammals and inhibition of this enzyme leads to the lowering of blood pressure.

Thiol group-containing amide or peptidyl amide-based metalloprotease (MMP) inhibitors are known as is shown in, for example, WO95/12389, WO96/11209 and U.S. 4,595,700. Hydroxamate group-

containing MMP inhibitors are disclosed in a number of published patent applications such as WO 95/29892, WO 97/24117, WO 97/49679 and EP 0 780 386 that disclose carbon back-boned compounds, and WO
5 90/05719, WO 93/20047, WO 95/09841 and WO 96/06074 that disclose hydroxamates that have a peptidyl back-bones or peptidomimetic back-bones, as does the article by Schwartz et al., *Progr. Med. Chem.*, 29:271-334(1992) and those of Rasmussen et al.,
10 *Pharmacol. Ther.*, 75(1): 69-75 (1997) and Denis et al., *Invest. New Drugs*, 15(3): 175-185 (1997).

One possible problem associated with known MMP inhibitors is that such compounds often exhibit the same or similar inhibitory effects against each
15 of the MMP enzymes. For example, the peptidomimetic hydroxamate known as batimastat is reported to exhibit IC₅₀ values of about 1 to about 20 nanomolar (nM) against each of MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9. Marimastat, another peptidomimetic
20 hydroxamate was reported to be another broad-spectrum MMP inhibitor with an enzyme inhibitory spectrum very similar to batimastat, except that marimastat exhibited an IC₅₀ value against MMP-3 of 230 nM. Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75
25 (1997).

Meta analysis of data from Phase I/II studies using marimastat in patients with advanced, rapidly progressive, treatment-refractory solid tumor cancers (colorectal, pancreatic, ovarian, prostate)
30 indicated a dose-related reduction in the rise of cancer-specific antigens used as surrogate markers for biological activity. Although marimastat exhibited some measure of efficacy via these markers,

toxic side effects were noted. The most common drug-related toxicity of marimastat in those clinical trials was musculoskeletal pain and stiffness, often commencing in the small joints in the hands,
5 spreading to the arms and shoulder. A short dosing holiday of 1-3 weeks followed by dosage reduction permits treatment to continue. Rasmussen et al.; *Pharmacol. Ther.*, 75(1): 69-75 (1997). It is thought that the lack of specificity of inhibitory effect
10 among the MMPs may be the cause of that effect.

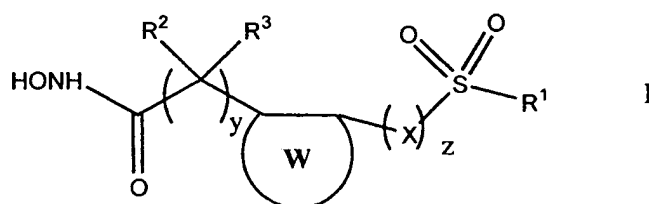
In view of the importance of hydroxamate MMP inhibitor compounds in the treatment of several diseases and the lack of enzyme specificity exhibited by two of the more potent drugs now in clinical
15 trials, it would be a great benefit if hydroxamates of greater enzyme specificity could be found. This would be particularly the case if the hydroxamate inhibitors exhibited strong inhibitory activity against one or more of MMP-2, MMP-9 or MMP-13 that
20 are associated with several pathological conditions, while at the same time exhibiting limited inhibition of MMP-1, an enzyme that is relatively ubiquitous and as yet not associated with any pathological condition. The disclosure that follows describes one
25 family of hydroxamate MMP inhibitors that exhibit those desirable activities

Brief Summary of the Invention

The present invention is directed to a
30 family of molecules that among other properties inhibit matrix metalloprotease (MMP) activity, and particularly inhibit the activity of one or more of MMP-2, MMP-9, or MMP-13, while generally exhibiting

little activity against MMP-1. The present invention is also directed to processes for preparing a contemplated compound and for treating a mammal having a condition associated with pathological matrix metalloprotease activity.

Briefly, one embodiment of the present invention is directed to a sulfonyl divalent aryl or heteroaryl hydroxamic acid compound that can act as a matrix metalloprotease enzyme inhibitor. That compound corresponds in structure to Formula I.



wherein

15

y and z are each zero or one and the sum of z+y is one;

the ring structure W is a 5- or 6-membered divalent aromatic or heteroaromatic ring;

20

X is -CH₂- or -NH-;

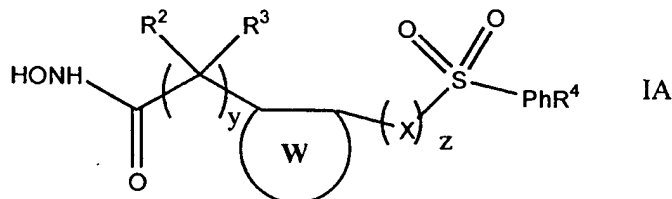
R¹ is a substituent containing a 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical bonded directly to the depicted SO₂-group and having a length greater than about that of a hexyl group and less than about that of a eicosyl group, said R¹ defining a three-dimensional volume, when rotated about an axis drawn through the SO₂-bonded 1-position and the 4-position of a 6-membered ring radical or drawn through the SO₂-bonded 1-position and the center of 3,4-bond of a 5-membered

ring radical, whose widest dimension in a direction transverse to the axis of rotation is about that of one furanyl ring to about that of two phenyl rings;

R^2 and R^3 are independently hydrido, C_1-C_4

5 hydrocarbyl, hydroxyl or amino, or R^2 and R^3 together with the depicted carbon atom to which they are bonded form a 6-membered heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally substituted with one or
 10 two oxygens when sulfur and being optionally substituted with a moiety selected from the group consisting of a C_1-C_4 hydrocarbyl, C_3-C_6 cyclohydrocarbyl, C_1-C_4 acylhydrocarbyl, and sulfonyl C_1-C_4 hydrocarbyl group when nitrogen.

15 In preferred embodiments, a contemplated compound corresponds in structure to Formula IA,



20 wherein W, X, y, z, R^2 and R^3 are as defined above, Ph is phenyl substituted at the 4-position with substituent R^4 that is defined hereinafter.

A process for treating a host mammal having a condition associated with pathological matrix metalloprotease activity is also contemplated. That
 25 process comprises administering a compound described hereinbefore in an enzyme-inhibiting effective amount to a mammalian host having such a condition. The use

of repeated administrations is particularly contemplated.

Among the several benefits and advantages of the present invention are the provision of
5 compounds and compositions effective as inhibitors of matrix metalloproteinase activity, and the provision of such compounds and compositions that are effective for the inhibition of metalloproteinases implicated in diseases and disorders involving uncontrolled
10 breakdown of connective tissue.

More particularly, a benefit of this invention is the provision of a compound and composition effective for inhibiting metalloproteinases, particularly MMP-13 and/or MMP-2,
15 associated with pathological conditions such as, for example, rheumatoid arthritis, osteoarthritis, septic arthritis, corneal, epidermal or gastric ulceration, tumor metastasis, invasion or angiogenesis, periodontal disease, proteinuria, Alzheimer's
20 Disease, coronary thrombosis and bone disease.

An advantage of the invention is the provision of a method for preparing such compositions. Another benefit is the provision of a method for treating a pathological condition
25 associated with abnormal matrix metalloproteinase activity.

Another advantage of the invention is the provision of compounds, compositions and methods effective for treating such pathological conditions
30 by selective inhibition of a metalloproteinase such as MMP-13 and MMP-2 associated with such conditions with minimal side effects resulting from inhibition

of other proteinases such as MMP-1, whose activity is necessary or desirable for normal body function.

Still further benefits and advantages of the invention will be apparent to the skilled worker
5 from the disclosure that follows.

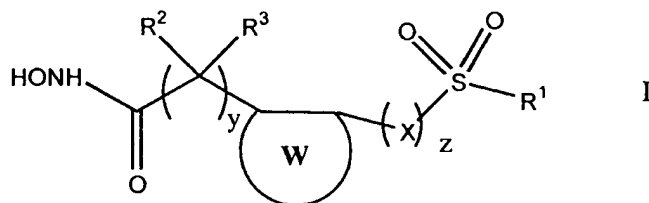
Detailed Description of Preferred Embodiments

In accordance with the present invention, it has been found that certain sulfonyl divalent aryl or
10 heteroaryl hydroxamic acids (hydroxamates) are effective, *inter alia*, for inhibition of matrix metalloproteinases ("MMPs") believed to be associated with uncontrolled or otherwise pathological breakdown of connective tissue. In particular, it has been
15 found that these certain sulfonyl divalent aryl or heteroaryl hydroxamic acid compounds are effective for inhibition of collagenase III (MMP-13) and also gelatinase A (MMP-2), which can be particularly destructive to tissue if present or generated in
20 abnormal quantities or concentrations, and thus exhibit a pathological activity.

Moreover, it has been discovered that many of these aromatic sulfonyl alpha-cycloamino hydroxamic acids are selective in the inhibition of
25 MMPs associated with diseased conditions without excessive inhibition of other collagenases essential to normal bodily function such as tissue turnover and repair. More particularly, it has been found that particularly preferred the sulfonyl divalent aryl or
30 heteroaryl hydroxamic acid compounds are particularly active in inhibiting of MMP-13 and/or MMP-2, while having a limited or minimal effect on MMP-1. This

point is discussed in detail hereinafter and is illustrated in the Inhibition Table hereinafter.

One embodiment of the present invention is directed to a sulfonyl divalent aryl or heteroaryl hydroxamic acid compound that can act as a matrix metalloprotease enzyme inhibitor. That compound corresponds in structure to Formula I



10

wherein

y and z are each zero or one and the sum of z+y is one;

15 the ring structure W is a 5- or 6-membered divalent aromatic or heteroaromatic ring;

X is -CH₂- or -NH-;

R¹ is a substituent containing a 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical bonded directly to the depicted SO₂-group and having a length equivalent to a length that is greater than about that of a fully extended hexyl group and less than about that of a fully extended eicosyl group, said R¹ defining a three-dimensional volume, when rotated about an axis drawn through the SO₂-bonded 1-position and the 4-position of a 6-membered ring radical or drawn through the SO₂-bonded 1-position and the center of 3,4-bond of a 5-membered ring radical, whose widest dimension in a direction transverse to the axis of rotation is about

that of one furanyl ring to about that of two phenyl rings;

R^2 and R^3 are independently hydrido, C_1-C_4 hydrocarbyl, hydroxyl or amino, or R^2 and R^3 together
5 with the depicted carbon atom to which they are bonded form a 6-membered heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally substituted with one or
10 substituted with a moiety selected from the group consisting of a C_1-C_4 hydrocarbyl, C_3-C_6 cyclohydrocarbyl, C_1-C_4 acylhydrocarbyl, and sulfonyl C_1-C_4 hydrocarbyl group when nitrogen.

In the above structural formula and other
15 formulas herein, one of y and z is one and the other is zero so that the sum of y plus z is one. Thus, either the $-CR^2R^3-$ or the $-CH_2-$ group of such formulas is absent in each contemplated compound.

The ring structure W is a 5- or 6-membered
20 divalent aromatic or heteroaromatic ring in which the depicted $-CR^2R^3-$ and $-CH_2-$ groups are bonded to adjacent carbon atoms of the aryl or heteroaryl ring. As a consequence, the hydroxamate carbonyl group and the R^1 -linked sulfonyl group are separated by three
25 carbon atoms in each contemplated compound.

Contemplated divalent aromatic or heteroaromatic rings include 1,2-phenylene, 2,3-pyridinylene, 3,4-pyridinylene, 4,5-pyridinylene, 2,3-pyrazinylene, 4,5-pyrimidinylene, and 5,6-pyrimidinylene groups. 1,2-Phenylene is a
30 particularly preferred divalent aromatic or

heteroaromatic ring, and is used illustratively herein as W.

As noted above, an R^1 substituent contains a 5- or 6-membered cyclohydrocarbyl, heterocyclo,
5 aryl or heteroaryl radical bonded directly to the depicted SO_2 -group. An R^1 substituent also has length, width and substitution requirements that are discussed in detail below. It is noted here, however, that a single- ringed or fused ring
10 cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical is not itself long enough to fulfill the length requirement. As such, that cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical must itself be substituted.

15 Exemplary 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radicals that can constitute a portion of a R^1 substituent and are themselves substituted as discussed herein include phenyl, 2-, 3-, or 4-
20 pyridyl, 2-naththyl, 2-pyrazinyl, 2- or 5-pyrimidinyl, 2- or 3-benzo(b)thienyl, 8-purinyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-imidazolyl, cyclopentyl, cyclohexyl, 2- or 3-piperidinyl, 2- or 3-morpholinyl, 2- or 3-tetrahydropyranyl, 2-
25 imidazolidinyl, 2- or 3-pyrazolidinyl and the like. A phenyl radical is particularly preferred and is used illustratively herein.

When examined along its longest chain of atoms, an R^1 substituent, including its own
30 substituent when present, has a total length equivalent to a length that is greater than that of a fully extended saturated chain of six carbon atoms (a

hexyl group); i.e., a length of a heptyl chain or longer, and a length that is less than that of a fully extended saturated chain of about 20 carbons (an eicosyl group). Preferably, that length is about
5 8 to about 18 carbon atoms, even though many more atoms may be present in ring structures or substituents. This length requirement is discussed further below.

Looked at more generally, and aside from
10 specific moieties from which it is constructed, an R^1 substituent (radical, group or moiety) has a length of a heptyl group or greater. Such an R^1 substituent also has a length that is less than that of an eicosyl group. That is to say that a R^1 is a
15 substituent having a length greater than that of a fully extended saturated six carbon chain and shorter than that of a fully extended saturated twenty carbon chain, and more preferably, a length greater than that of a octyl group and less than that of a
20 palmityl group. The radical chain lengths are measured along the longest linear atom chain in the radical, following the skeletal atoms of a ring where necessary. Each atom in the chain, e.g. carbon, oxygen or nitrogen, is presumed to be carbon for ease
25 in calculation.

Such lengths can be readily determined by using published bond angles, bond lengths and atomic radii, as needed, to draw and measure a chain, or by building models using commercially available kits
30 whose bond angles, lengths and atomic radii are in accord with accepted, published values. Radical (substituent) lengths can also be determined somewhat less exactly by presuming, as is done here, that all

atoms have bond lengths of saturated carbon, that unsaturated and aromatic bonds have the same lengths as saturated bonds and that bond angles for unsaturated bonds are the same as those for saturated bonds, although the above-mentioned modes of measurement are preferred. For example, a 4-phenyl or 4-pyridyl group has a length of a four carbon chain, as does a propoxy group, whereas a biphenyl group has a length of about an eight carbon chain using a contemplated measurement mode.

In addition, an R^1 substituent, when rotated about an axis drawn through the SO_2 -bonded 1-position and the 4-position of a 6-membered ring radical or the SO_2 -bonded 1-position and through the 3,4 bond of a 5-membered ring radical defines a three-dimensional volume whose widest dimension has the width of about one furanyl ring to about the width of two phenyl rings in a direction transverse to that axis to rotation.

When utilizing this width or volume criterion, a fused ring system such as a naphthyl or purinyl radical is considered to be a 6- or 5-membered ring that is substituted at appropriate positions numbered from the SO_2 -linkage that is deemed to be at the 1-position as discussed before. Thus, a 2-naphthyl substituent or an 8-purinyl substituent is an appropriately sized R^1 radical as to width when examined using the above rotational width criterion. On the other hand, a 1-naphthyl group or a 7- or 9-purinyl group is too large upon rotation and is excluded.

As a consequence of these length and width requirements, R¹ substituents such as
4-(phenyl)phenyl [biphenyl],
4-(4'-methoxyphenyl)phenyl, 4-(phenoxy)phenyl,
5 4-(thiophenyl)phenyl [4-(phenylthio)phenyl],
4-(phenylazo)phenyl 4-(phenylureido)phenyl, 4-
(anilino)phenyl, 4-(nicotinamido)phenyl, 4-
(isonicotinamido)phenyl, 4-(picolinamido)phenyl and
4-(benzamido)phenyl are among particularly preferred
10 R¹ substituents, with 4-(phenoxy)phenyl and
4-(thiophenyl)phenyl being most preferred.

An SO₂-linked cyclohydrocarbyl,
heterocyclo, aryl or heteroaryl radical is a 5- or
6-membered single-ring that is itself substituted
15 with one other substituent, R⁴. The SO₂-linked
single-ringed cyclohydrocarbyl, heterocyclo, aryl or
heteroaryl radical is R⁴-substituted at its own
4-position when a 6-membered ring and at its own
3-position when a 5-membered ring. The
20 cyclohydrocarbyl, heterocyclo, aryl or heteroaryl
radical to which R⁴ is bonded is preferably a phenyl
group, so that R¹ is preferably PhR⁴ in which R⁴ is
bonded at the 4-position of the SO₂-linked phenyl
(Ph) radical, and in which R⁴ can itself be
25 optionally substituted as is discussed hereinafter.
Substitution at the 2-position of a SO₂-linked
cyclohydrocarbyl, heterocyclo, aryl or heteroaryl
radical appears to greatly lessen inhibitory potency
toward MMP enzymes, and is absent from a contemplated
30 compound.

A contemplated R⁴ substituent can be a
single-ringed cyclohydrocarbyl, heterocyclo, aryl or

heteroaryl group or another substituent having a chain length of 3 to about 14 carbon atoms such as a hydrocarbyl or hydrocarbyloxy group [e.g., C₃-C₁₄ hydrocarbyl or O-C₂-C₁₄ hydrocarbyl], a phenyl group, a phenoxy group [-OC₆H₅], a thiophenoxy group [phenylsulfanyl; -SC₆H₅], an anilino group [-NHC₆H₅], a phenylazo group [-N₂C₆H₅], a phenylureido group [aniline carbonylamino; -NHC(O)NH-C₆H₅], a benzamido group [-NHC(O)C₆H₅], a nicotinamido group [3-NHC(O)C₅H₄N], an isonicotinamido group [4-NHC(O)C₅H₄N], or a picolinamido group [2-NHC(O)C₅H₄N]. As noted before in conjunction with the discussion of R¹, most preferred R⁴ substituents are phenoxy and thiophenoxy groups that are preferably themselves free of substitution. Additionally contemplated R⁴ substituent groups include a heterocyclo, heterocyclohydrocarbyl, arylhydrocarbyl, arylheterocyclohydrocarbyl, heteroarylhydrocarbyl, heteroarylheterocyclohydrocarbyl, arylhydrocarbyloxyhydrocarbyl, aryloxyhydrocarbyl, hydrocarboylhydrocarbyl, arylhydrocarboylhydrocarbyl, arylcarbonylhydrocarbyl, arylazoaryl, arylhydrazinoaryl, hydrocarbylthiohydrocarbyl, hydrocarbylthioaryl, arylthiohydrocarbyl, heteroarylthiohydrocarbyl, hydrocarbylthioarylhydrocarbyl, arylhydrocarbylthiohydrocarbyl, arylhydrocarbylthioaryl, arylhydrocarbylamino, heteroarylhydrocarbylamino, or a heteroarylthio group.

A contemplated R⁴ substituent can itself also be substituted with one or more substituent radicals at the meta- or para-position or both of a six-membered ring with a single atom or a substituent
5 containing a longest chain of up to ten atoms, excluding hydrogen. Exemplary substituent radicals include a halo, hydrocarbyl, hydrocarbyloxy, nitro, cyano, perfluorohydrocarbyl, trifluoromethylhydrocarbyl, hydroxy, mercapto,
10 hydroxycarbonyl, aryloxy, arylthio, arylamino, arylhydrocarbyl, aryl, heteroaryloxy, heteroarylthio, heteroarylamino, heteroarhydrocarbyl, hydrocarbyloxycarbonylhydrocarbyl, heterocyclooxy, hydroxycarbonylhydrocarbyl, heterocyclothio,
15 heterocycloamino, cyclohydrocarbyloxy, cyclohydrocarbylthio, cyclohydrocarbylamino, heteroarylhydrocarbyloxy, heteroarylhydrocarbylthio, heteroarylhydrocarbylamino, arylhydrocarbyloxy, arylhydrocarbylthio, arylhydrocarbylamino,
20 heterocyclic, heteroaryl, hydroxycarbonylhydrocarbyloxy, alkoxycarbonylalkoxy, hydrocarbyloyl, arylcarbonyl, arylhydrocarbyloyl, hydrocarbyloxy, arylhydrocarbyloxy, hydroxyhydrocarbyl, hydroxyhydrocarbyloxy, hydrocarbylthio,
25 hydrocarbyloxyhydrocarbylthio, hydrocarbyloxycarbonyl, hydroxycarbonylhydrocarbyloxy, hydrocarbyloxy-carbonylhydrocarbyl, hydrocarbylhydroxycarbonylhydrocarbylthio,
30 hydrocarbyloxycarbonylhydrocarbyloxy, hydrocarbyloxycarbonylhydrocarbylthio, amino, hydrocarbylcarbonylamino, arylcarbonylamino, cyclohydrocarbylcarbonylamino,

heterocyclohydrocarbylcarbonylamino,
arylhydrocarbylcarbonylamino,
heteroarylcarbonylamino,
heteroarylhydrocarbylcarbonylamino,
5 heterocyclohydrocarbyloxy, hydrocarbylsulfonylamino,
arylsulfonylamino, arylhydrocarbylsulfonylamino,
heteroarylsulfonylamino, heteroarylhydrocarbyl-
sulfonylamino, cyclohydrocarbylsulfonylamino,
heterocyclohydrocarbylsulfonylamino and N-
10 monosubstituted or N,N-disubstituted aminohydrocarbyl
group wherein the substituent(s) on the nitrogen are
selected from the group consisting of hydrocarbyl,
aryl, arylhydrocarbyl, cyclohydrocarbyl,
arylhydrocarbyloxy, hydrocarbyloxy, hydrocarbyloxy,
15 and hydrocarbyl, or wherein the nitrogen and two
substituents attached thereto form a 5- to 8-membered
heterocyclic or heteroaryl ring group.

Thus, initial studies indicate that so long
as the length, substitution and width (volume upon
20 rotation) requirements of an SO₂-linked R¹
substituent discussed herein are met, an R¹
substituent can be extremely varied.

A particularly preferred R⁴ substituent of
an SO₂-linked Ph group is a single-ringed aryl or
25 heteroaryl, phenoxy, thiophenoxy, phenylazo,
phenylureido, nicotinamido, isonicotinamido,
picolinamido, anilino or benzamido group that is
unsubstituted or is itself substituted (optionally
substituted) at the para-position when a 6-membered
30 ring or the 3-position when a 5-membered ring. Here,
single atoms such as halogen moieties or substituents
that contain one to a chain of about ten atoms other

than hydrogen such as C₁-C₁₀ hydrocarbyl, C₁-C₉ hydrocarbyloxy or carboxyethyl groups can be used.

Exemplary particularly preferred PhR⁴

(particularly preferred R¹) substituents include

5 biphenyl, 4-phenoxyphenyl, 4-thiophenoxyphenyl, 4-benzamidophenyl, 4-phenylureido, 4-anilinophenyl, 4-nicotinamido, 4-isonicotinamido, and 4-picolinamido. Exemplary particularly preferred R⁴ groups contain a 6-membered aromatic ring and include a phenyl group,
10 a phenoxy group, a thiophenoxy group, a phenylazo group, a phenylureido group, an anilino group, a nicotinamido group, an isonicotinamido group, a picolinamido group and a benzamido group.

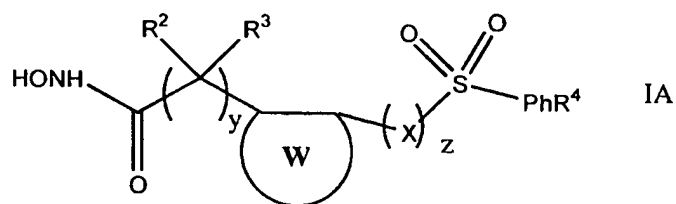
More specifically, a particularly preferred
15 sulfonyl butanhydroxamate compounds has an R⁴ substituent that is a phenyl group, a phenoxy group, a thiophenoxy group, a phenylazo group, a phenylureido group, an anilino group, a nicotinamido group, an isonicotinamido group, a picolinamido group
20 or a benzamido group that is itself optionally substituted at its own meta or para-position or both with a moiety that is selected from the group consisting of a halogen, a C₁-C₉ hydrocarbyloxy (-O-C₁-C₉ hydrocarbyl) group, a C₁-C₁₀ hydrocarbyl group,
25 a di-C₁-C₉ hydrocarbylamino [-N(C₁-C₉ hydrocarbyl)(C₁-C₉ hydrocarbyl)] group, a carboxyl C₁-C₈ hydrocarbyl (C₁-C₈ hydrocarbyl-CO₂H) group, a C₁-C₄ hydrocarbyloxy carbonyl C₁-C₄ hydrocarbyl [C₁-C₄ hydrocarbyl-O-(CO)-C₁-C₄ hydrocarbyl] group, a C₁-
30 C₄ hydrocarbyloxycarbonyl C₁-C₄ hydrocarbyl [C₁-C₄ hydrocarbyl(CO)-O-C₁-C₄ hydrocarbyl] group and a C₁-

C₈ hydrocarbyl carboxamido [-NH(CO)-C₁-C₈ hydrocarbyl] group, or is substituted at the meta- and para-positions by two methyl groups or by a C₁-C₂ alkylenedioxy group such as a methylenedioxy group.

5 Inasmuch as a contemplated SO₂-linked cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical is itself preferably substituted with a 6-membered aromatic ring, two nomenclature systems are used together herein for ease in understanding
10 substituent positions. The first system uses position numbers for the ring directly bonded to the SO₂-group, whereas the second system uses ortho, meta or para for the position of one or more substituents of a 6-membered ring bonded to a SO₂-linked
15 cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical. When a R⁴ substituent is other than a 6-membered ring, substituent positions are numbered from the position of linkage to the aromatic or heteroaromatic ring. Formal chemical nomenclature is
20 used in naming particular compounds.

 Thus, the 1-position of an above-discussed SO₂-linked cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical is the position at which the SO₂-group is bonded to the ring. The 4- and 3-positions
25 of rings discussed here are numbered from the sites of substituent bonding from the SO₂-linkage as compared to formalized ring numbering positions used in heteroaryl nomenclature.

30



In preferred embodiments, a contemplated
 5 compound corresponds in structure to Formula IA,
 wherein W, X, y, z, R² and R³ are as defined above,
 Ph is phenyl substituted at the 4-position with
 substituent R⁴ that is defined hereinabove.

R² and R³ substituents are independently
 10 selected.

Those groups can be hydrido, C₁-C₄ hydrocarbyl such
 as methyl, ethyl, propyl, allyl, propargyl, butyl and
 but-2-ynyl and the like, hydroxyl or amino.

In addition, R² and R³ together with the
 15 depicted carbon atom to which they are bonded can
 form a 6-membered heterocyclic ring in which the
 heteroatom is oxygen, sulfur or nitrogen. That
 heteroatom is optionally substituted with one or two
 oxygens when sulfur, and when nitrogen is optionally
 20 substituted with a moiety (R⁵) selected from the
 group consisting of a C₁-C₄ hydrocarbyl (as above),
 C₃-C₆ cyclohydrocarbyl such as cyclopropyl,
 cyclobutyl, cyclopentenyl and cyclohexenyl, C₁-C₄
 acylhydrocarbyl such as formyl, acetyl, acrylyl, and
 25 butyryl, and a sulfonyl C₁-C₄ hydrocarbyl group such
 as methylsulfonyl, ethylsulfonyl and the like. Thus,
 R² and R³ together can form a 4-tetrahydrothiopyranyl
 group, its corresponding sulfoxide or sulfone, a 4-

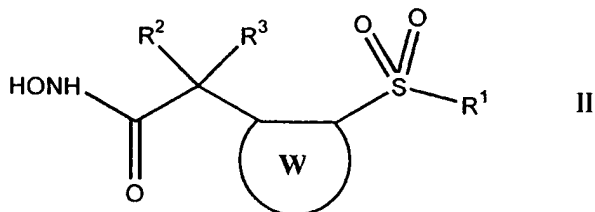
piperidinyl or a 4-tetrahydropyranyl group. When present, the 4-piperidinyl group can be N-substituted with an above-described R⁵ substituent.

5 The length of a R¹ substituent bonded to the SO₂ group is believed to play a role in the overall activity of a contemplated inhibitor compound against MMP enzymes generally. Thus, a compound having an R¹ substituent that is shorter in length than a heptyl group, e.g., a 4-methoxyphenyl group
10 (compound of Example 6), typically exhibits moderate to poor inhibitory activity against all of the MMP enzymes, whereas compounds whose R¹ substituents have a length of about an heptyl chain or longer, e.g., a 4-phenoxyphenyl group (compound of Example 1) that
15 has a length of about a nine-carbon chain, typically exhibit good to excellent potencies against MMP-13 or MMP-2 and also selectivity against MMP-1. Exemplary data are provided in Table 32 hereinafter in which the activities of the above two compounds can be
20 compared.

The data of Table 32 also illustrate that compounds of seemingly similar structure are not particularly effective inhibitors of the activity of MMP-13. Thus, those data indicate that the before-
25 noted spacing of three carbon atoms between the carbonyl of the hydroxamate and the sulfonyl group has some criticality for these compounds and that the third carbon cannot be replaced by an amido nitrogen atom.

30 In view of the above-discussed preferences, compounds corresponding in structure to particular formulas constitute particularly preferred embodiments.

In one of those embodiments, a contemplated compound corresponds in structure to Formula II, below,

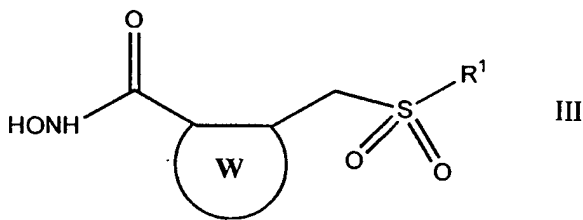


5

wherein W, R¹, R², and R³ are as defined above, and R¹ is preferably PhR⁴, as is also defined above.

10

In another of those embodiments, a contemplated compound corresponds in structure to Formula III, below,

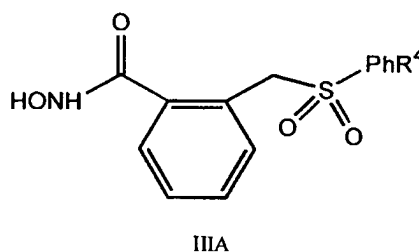
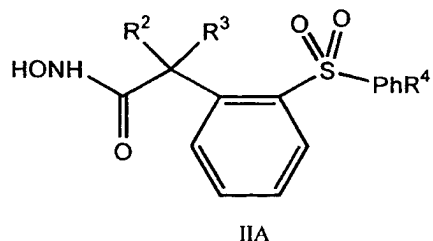


15

wherein W, R¹, R², and R³ are as defined above, and R¹ is preferably PhR⁴, as is also defined above.

20

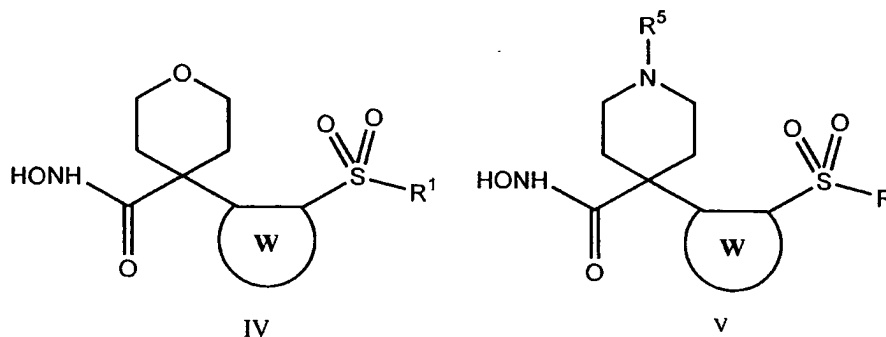
Taking into account the before-stated preference that W be a 1,2-phenylene radical and the preference for R¹ being PhR⁴, particularly preferred compounds of Formulas II and III correspond in structure to Formulas IIA and IIIA, below,



wherein the above definitions for R^2 , R^3 and PhR^4 also apply.

5 In yet another group of preferred compounds, R^2 and R^3 together with the carbon atom to which they are bonded form a 4-piperidinyl or tetrahydropyranyl group in which the nitrogen of the 4-piperidinyl group is optionally substituted with a moiety R^5 selected from the group consisting of a C_1 - C_4 hydrocarbyl, C_3 - C_6 cyclohydrocarbyl, C_1 - C_4 acylhydrocarbyl, and a sulfonyl C_1 - C_4 hydrocarbyl group. Those preferred compounds correspond in

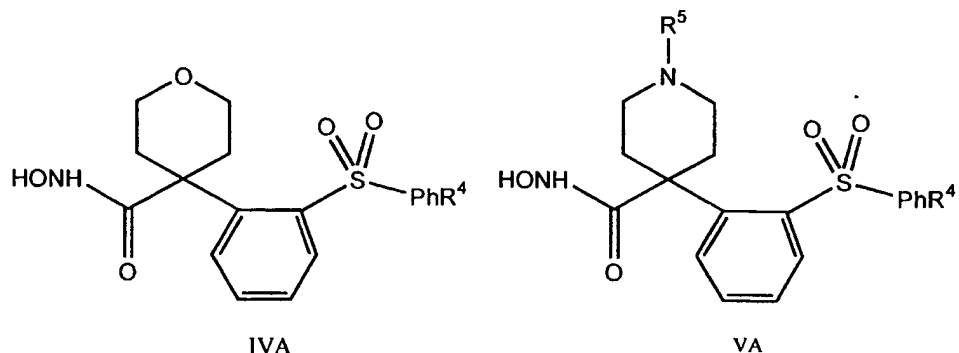
15



wherein R^1 is as defined above, and is preferably PhR^4 , as is also defined above.

20 Again taking into account the before-stated preference that W be a 1,2-phenylene radical and the preference for R^1 being PhR^4 , particularly preferred

compounds of Formulas IV and V correspond in structure to Formulas IVA and VA, below, wherein the above definitions for R⁵ and PhR⁴ also apply.



The word "hydrocarbyl" is used herein as a short hand term to include straight and branched chain aliphatic as well as alicyclic groups or radicals that contain only carbon and hydrogen. Thus, alkyl, alkenyl and alkynyl groups are contemplated, whereas aromatic hydrocarbons such as phenyl and naphthyl groups, which strictly speaking are also hydrocarbyl groups, are referred to herein as aryl groups or radicals, as discussed hereinafter. Where a specific aliphatic hydrocarbyl substituent group is intended, that group is recited; i.e., C₁-C₄ alkyl, methyl or dodecenyl. Exemplary hydrocarbyl groups contain a chain of 1 to about 12 carbon atoms, and preferably one to about 10 carbon atoms.

A particularly preferred hydrocarbyl group is an alkyl group. As a consequence, a generalized, but more preferred substituent can be recited by replacing the descriptor "hydrocarbyl" with "alkyl" in any of the substituent groups enumerated herein.

Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl,

sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like. Examples of suitable alkenyl radicals include ethenyl (vinyl), 2-propenyl, 3-propenyl, 1,4-pentadienyl, 1,4-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, decenyl and the like. Examples of alkynyl radicals include ethynyl, 2-propynyl, 3-propynyl, decynyl, 1-butyne, 2-butyne, 3-butyne, and the like.

Usual chemical suffix nomenclature is followed when using the word "hydrocarbyl" except that the usual practice of removing the terminal "yl" and adding an appropriate suffix is not always followed because of the possible similarity of a resulting name to one or more substituents. Thus, a hydrocarbyl ether is referred to as a "hydrocarbyloxy" group rather than a "hydrocarboxy" group as may possibly be more proper when following the usual rules of chemical nomenclature. On the other hand, a hydrocarbyl group containing a -C(O)O- functionality is referred to as a hydrocarboxyl group inasmuch as there is no ambiguity in using that suffix. As a skilled worker will understand, a substituent that cannot exist such as a C₁ alkenyl group is not intended to be encompassed by the word "hydrocarbyl".

The term "carbonyl", alone or in combination, means a -C(=O)- group wherein the remaining two bonds (valences) are independently substituted. The term "thiol" or "sulfhydryl", alone or in combination, means a -SH group. The term "thio" or "thia", alone or in combination, means a thiaether group; i.e., an ether group wherein the ether oxygen is replaced by a sulfur atom.

The term "amino", alone or in combination, means an amine or -NH_2 group, whereas the term mono-substituted amino, alone or in combination, means a substituted amine $\text{-N(H)(substituent)}$ group wherein
5 one hydrogen atom is replaced with a substituent, and disubstituted amine means a -N(substituent)_2 wherein two hydrogen atoms of the amino group are replaced with independently selected substituent groups.
Amines, amino groups and amides are classes that can
10 be designated as primary (I°), secondary (II°) or tertiary (III°) or unsubstituted, mono-substituted or di-substituted depending on the degree of substitution of the amino nitrogen. Quaternary amine (IV°) means a nitrogen with four substituents ($\text{-N}^+(\text{substituent})_4$) that is positively charged and
15 accompanied by a counter ion or N-oxide means one substituent is oxygen and the group is represented as ($\text{-N}^+(\text{substituent})_3\text{-O}^-$); i.e., the charges are internally compensated.

20 The term "cyano", alone or in combination, means a $\text{-C-triple bond-N (-CN)}$ group. The term "azido", alone or in combination, means an $\text{-N-double bond-N-double bond-N- (-N=N=N-)}$.

The term "hydroxyl", alone or in
25 combination, means a -OH group. The term "nitro", alone or in combination, means a -NO_2 group.

The term "azo", alone or in combination, means a -N=N- group wherein the bonds at the terminal positions are independently substituted. The term
30 "hydrazino", alone or in combination, means a -NH-NH- group wherein the remaining two bonds (valences) are independently substituted. The hydrogen atoms of the hydrazino group can be replaced, independently, with

substituents and the nitrogen atoms can form acid addition salts or be quaternized.

The term "sulfonyl", alone or in combination, means a $-S(O)_2-$ group wherein the
5 remaining two bonds (valences) can be independently substituted. The term "sulfoxido", alone or in combination, means a $-S(=O)_1-$ group wherein the remaining two bonds (valences) can be independently substituted. The term "sulfonamide", alone or in
10 combination, means a $-S(=O)_2-N=$ group wherein the remaining three bonds (valences) are independently substituted. The term "sulfinamido", alone or in combination, means a $-S(=O)_1N=$ group wherein the remaining three bonds (valences) are independently
15 substituted. The term "sulfenamide", alone or in combination, means a $-S-N=$ group wherein the remaining three bonds (valences) are independently substituted.

The term "hydrocarbyloxy", alone or in
20 combination, means an hydrocarbyl ether radical wherein the term hydrocarbyl is as defined above. Examples of suitable hydrocarbyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, allyloxy, n-butoxy, iso-butoxy, sec-butoxy, tert-
25 butoxy and the like. The term "cyclohydrocarbyl", alone or in combination, means a hydrocarbyl radical that contains 3 to about 8 carbon atoms, preferably from about 3 to about 6 carbon atoms, and is cyclic. The term "cyclohydrocarbylhydrocarbyl" means an
30 hydrocarbyl radical as defined above which is substituted by a cyclohydrocarbyl as also defined above. Examples of such cyclohydrocarbylhydrocarbyl

radicals include cyclopropyl, cyclobutyl, cyclopentenyl, cyclohexyl cyclooctynyl and the like.

The term "aryl", alone or in combination, means a phenyl or naphthyl radical that optionally carries one or more substituents selected from hydrocarbyl, hydrocarbyloxy, halogen, hydroxy, amino, nitro and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, and the like. The term "arylhydrocarbyl", alone or in combination, means an hydrocarbyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, 2-phenylethyl and the like. The term "arylhydrocarbyloxycarbonyl", alone or in combination, means a radical of the formula $-C(O)-O-$ arylhydrocarbyl in which the term "arylhydrocarbyl" has the significance given above. An example of an arylhydrocarbyloxycarbonyl radical is benzyloxycarbonyl. The term "aryloxy" means a radical of the formula aryl-O- in which the term aryl has the significance given above. The term "aromatic ring" in combinations such as substituted-aromatic ring sulfonamide, substituted-aromatic ring sulfinamide or substituted-aromatic ring sulfenamide means aryl or heteroaryl as defined above.

The terms "hydrocarbyloyl" or "hydrocarbylcarbonyl", alone or in combination, mean an acyl radical derived from an hydrocarbylcarboxylic acid, examples of which include acetyl, propionyl, acryloyl, butyryl, valeryl, 4-methylvaleryl, and the like. The term "cyclohydrocarbylcarbonyl" means an acyl group derived from a monocyclic or bridged

cyclohydrocarbylcarboxylic acid such as cyclopropanecarbonyl, cyclohexenecarbonyl, adamantanecarbonyl, and the like, or from a benz-fused monocyclic cyclohydrocarbylcarboxylic acid that
5 is optionally substituted by, for example, a hydrocarbyloylamino group, such as 1,2,3,4-tetrahydro-2-naphthoyl, 2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl. The terms "arylhydrocarbyloyl" or "arylhydrocarbylcarbonyl"
10 mean an acyl radical derived from an aryl-substituted hydrocarbylcarboxylic acid such as phenylacetyl, 3-phenylpropenyl (cinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminocinnamoyl, 4-methoxycinnamoyl and the like.
15 The terms "aroyl" or "arylcarbonyl" means an acyl radical derived from an aromatic carboxylic acid. Examples of such radicals include aromatic carboxylic acids, an optionally substituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl,
20 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like.
25 The heterocyclyl (heterocyclo) or heterocyclohydrocarbyl portion of a heterocyclylcarbonyl, heterocyclioxycarbonyl, heterocyclylhydrocarbyloxycarbonyl, or heterocyclohydrocarbyl group or the like is a
30 saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle that contains one to four hetero atoms selected from nitrogen, oxygen and sulphur, which is optionally substituted on one

or more carbon atoms by a halogen, alkyl, alkoxy, oxo group, and the like, and/or on a secondary nitrogen atom (i.e., -NH-) by an hydrocarbyl, arylhydrocarbyloxycarbonyl, hydrocarbyloyl, aryl or
5 arylhydrocarbyl or on a tertiary nitrogen atom (i.e. =N-) by oxido and that is attached via a carbon atom. The tertiary nitrogen atom with three substituents can also form a N-oxide
[=N(O)-] group. Examples of such heterocyclyl groups
10 are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, and the like.

The heteroaryl portion of a heteroaryl, heteroaryloxycarbonyl, or a heteroarylhydrocarbyloyl (heteroarylhydrocarbyl carbonyl) group or the like is
15 an aromatic monocyclic, bicyclic, or tricyclic heterocycle that contains the hetero atoms and is optionally substituted as defined above with respect to the definition of heterocyclyl. A "heteroaryl" group is an aromatic heterocyclic ring substituent
20 that can contain one, two, three or four atoms in the ring that are other than carbon. Those heteroatoms can be nitrogen, sulfur or oxygen. A heteroaryl group can contain a single five- or 6-membered ring or a fused ring system that contains two 6-membered
25 rings or a five- and a 6-membered ring. Exemplary heteroaryl groups include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as 1,3,5-, 1,2,4- or 1,2,3-triazinyl, imidazyl, furanyl,
30 thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl groups ; six/5-membered fused ring substituents such as benzothiofuranyl,

isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl and anthranilyl groups ; and six/6-membered fused rings such as 1,2-, .1,4-, .2,3- and 2,1-benzopyronyl, quinolinyl, isoquinolinyl, cinnolinyl, 5 quinazolinyl, and 1,4-benzoxazinyl groups.

The term "cyclohydrocarbylhydrocarbyloxy-carbonyl" means an acyl group derived from a cyclohydrocarbylhydrocarbyloxycarboxylic acid of the formula cyclohydrocarbylhydrocarbyl-O-COOH wherein 10 cyclohydrocarbylhydrocarbyl has the significance given above. The term "aryloxyhydrocarbyloyl" means an acyl radical of the formula aryl-O-hydrocarbyloyl wherein aryl and hydrocarbyloyl have the significance given above. The term "heterocyclyloxycarbonyl" 15 means an acyl group derived from heterocyclyl-O-COOH wherein heterocyclyl is as defined above. The term "heterocyclylhydrocarbyloyl" is an acyl radical derived from a heterocyclyl-substituted hydrocarbylcarboxylic acid wherein heterocyclyl has 20 the significance given above. The term "heterocyclylhydrocarbyloxycarbonyl" means an acyl radical derived from a heterocyclyl-substituted hydrocarbyl-O-COOH wherein heterocyclyl has the significance given above. The term 25 "heteroaryloxycarbonyl" means an acyl radical derived from a carboxylic acid represented by heteroaryl-O-COOH wherein heteroaryl has the significance given above.

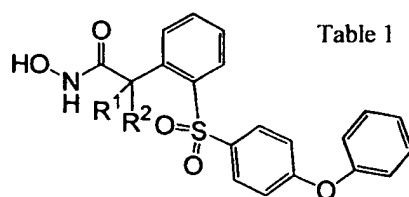
The term "aminocarbonyl" alone or in 30 combination, means an amino-substituted carbonyl (carbamoyl) group derived from an amino-substituted carboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing

substituents selected from hydrogen, hydrocarbyl, aryl, aralkyl, cyclohydrocarbyl, cyclohydrocarbylhydrocarbyl radicals and the like. The term "aminohydrocarbyloyl" means an acyl group
5 derived from an amino-substituted hydrocarbylcarboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents independently selected from hydrogen, alkyl, aryl, aralkyl, cyclohydrocarbyl,
10 cyclohydrocarbylhydrocarbyl radicals and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine. The term "halohydrocarbyl" means a hydrocarbyl radical having the significance as defined above wherein one or more
15 hydrogens are replaced with a halogen. Examples of such halohydrocarbyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like. The term perfluorohydrocarbyl means a hydrocarbyl
20 group wherein each hydrogen has been replaced by a fluorine atom. Examples of such perfluorohydrocarbyl groups, in addition to trifluoromethyl above, are perfluorobutyl, perfluoroisopropyl, perfluorododecyl and perfluorodecyl.

25 Table 1 through Table 31, below, show several contemplated sulfonyl divalent aryl or heteroaryl hydroxamic acid compounds as structural formulas that illustrate substituent groups. Each group of compounds is illustrated by a generic
30 formula, followed by a series of preferred moieties or groups that constitute various substituents that can be attached at the position clearly shown in the generic structure. The substituent symbols, e.g.,

R¹, R² X, are as shown in each Table, and are different from those shown elsewhere herein in structural formulas bearing Roman numerals. One or two bonds (straight lines) are shown with those
5 substituents to indicate the respective positions of attachment in the illustrated compound. This system is well known in the chemical communication arts and is widely used in scientific papers and presentations.



Example	R ¹	R ²	Example	R ¹	R ²	Example	R ¹	R ²
1	-H	-H	13			20		
2	-H	-CH ₃						
3	-CH ₃	-CH ₃				21		
4	-H	-OH	14					
5	-CH ₃	-OH						
6			15					
7						22		
8			16					
9						23		
10			17					
11								
12			18			24		
			19					



Table 2

Example	R ¹	R ²	Example	R ¹	R ²	Example	R ¹	R ²
1	-H	-H	13			20		
2	-H	-CH ₃						
3	-CH ₃	-CH ₃	14			21		
4	-H	-OH						
5	-CH ₃	-OH	15			22		
6			16			23		
7			17					
8			18			24		
9			19					
10								
11								
12								

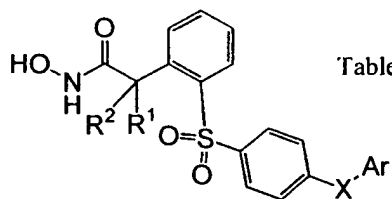

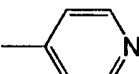

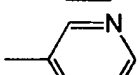

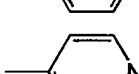

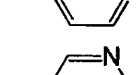

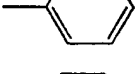

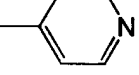

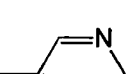

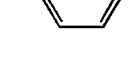

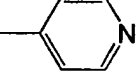

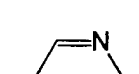


Table 3

Example	R ¹	R ²	X	Ar
1			O	
2			O	
3			O	
4			O	
5			O	
6			O	
7			O	
8			O	
9			S	
10			S	

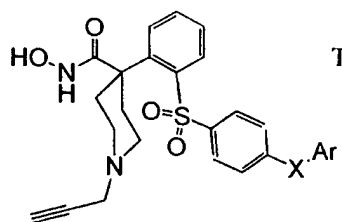


Table 4

Example	X	Ar	Example	X	Ar
1	O		12	S	
2	O		13	S	
3	O		14	S	
4	O		15	S	
5	O		16	S	
6	O		17	S	
7	O		18	S	
8	O		19	S	
9	O		20	S	
10	O		21	S	
11	O		22	S	

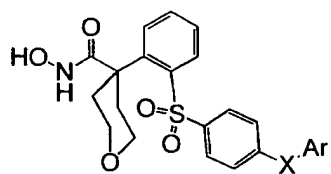
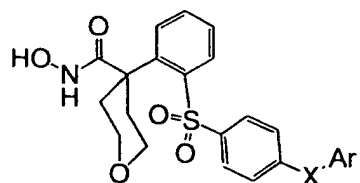


Table 5

Example	X	Ar	Example	X	Ar
1	O		12	S	
2	O		13	S	
3	O		14	S	
4	O		15	S	
5	O		16	S	
6	O		17	S	
7	O		18	S	
8	O		19	S	
9	O		20	S	
10	O		21	S	
11	O		22	S	

Table 6



Example X	Ar	Example X	Ar
1	O	9	S
2	O	10	S
3	O	11	S
4	O	12	S
5	O	13	S
6	O	14	S
7	O	15	S
8	O	16	S

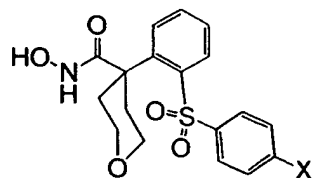


Table 7

Example	X	Example	X
1		11	
2		12	
3		13	
4		14	
5		15	
6		16	
7		17	
8		18	
9		19	
10		20	

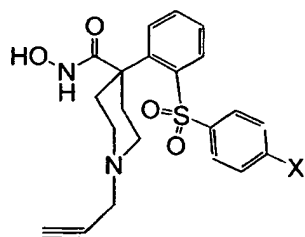


Table 8

Example	X	Example	X
1		11	
2		12	
3		13	
4		14	
5		15	
6		16	
7		17	
8		18	
9		19	
10		20	

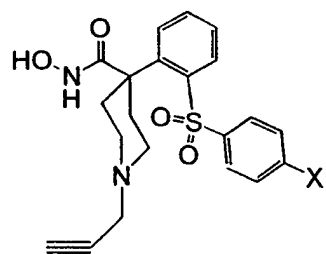


Table 9

Example	X	Example	X
1		9	
2		10	
3		11	
4		12	
5		13	
6		14	
7		15	
8		16	

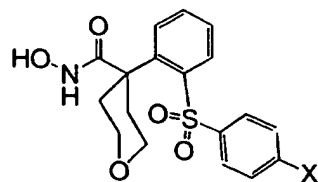


Table 10

Example	X	Example	X
1		9	
2		10	
3		11	
4		12	
5		13	
6		14	
7		15	
8		16	

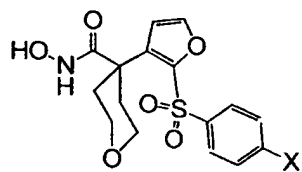


Table 11

Example	X	Example	X
1		9	
2		10	
3		11	
4		12	
5		13	
6		14	
7		15	
8		16	

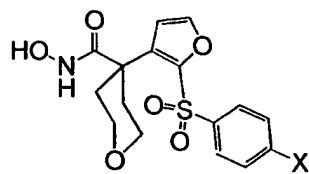
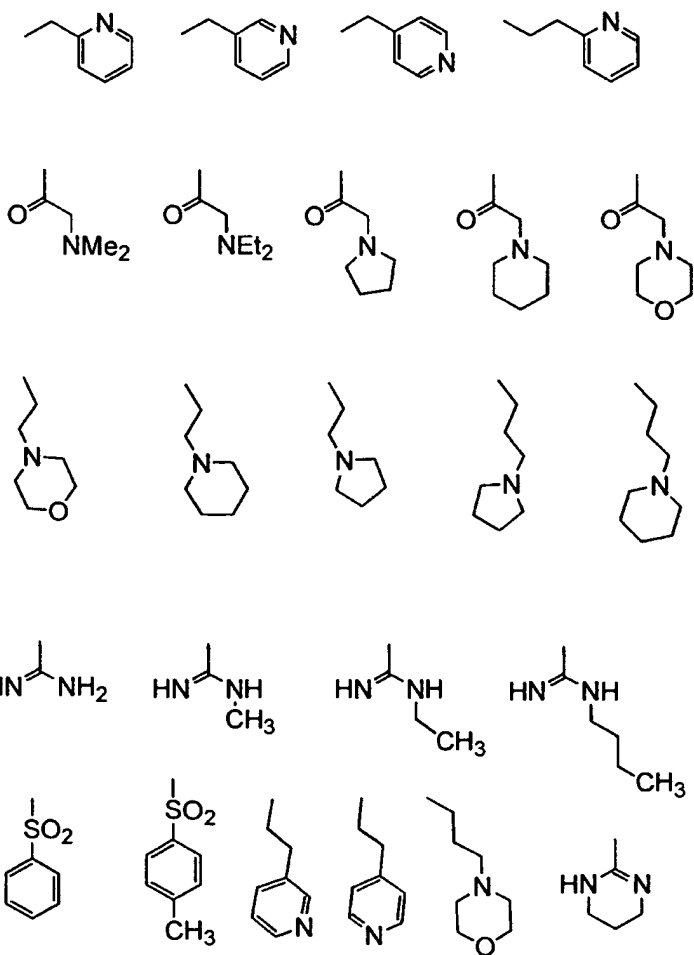
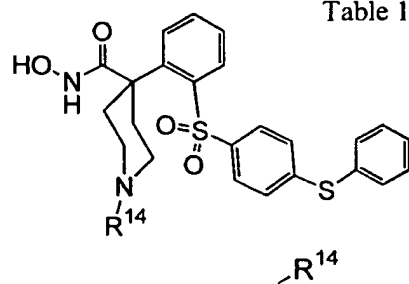
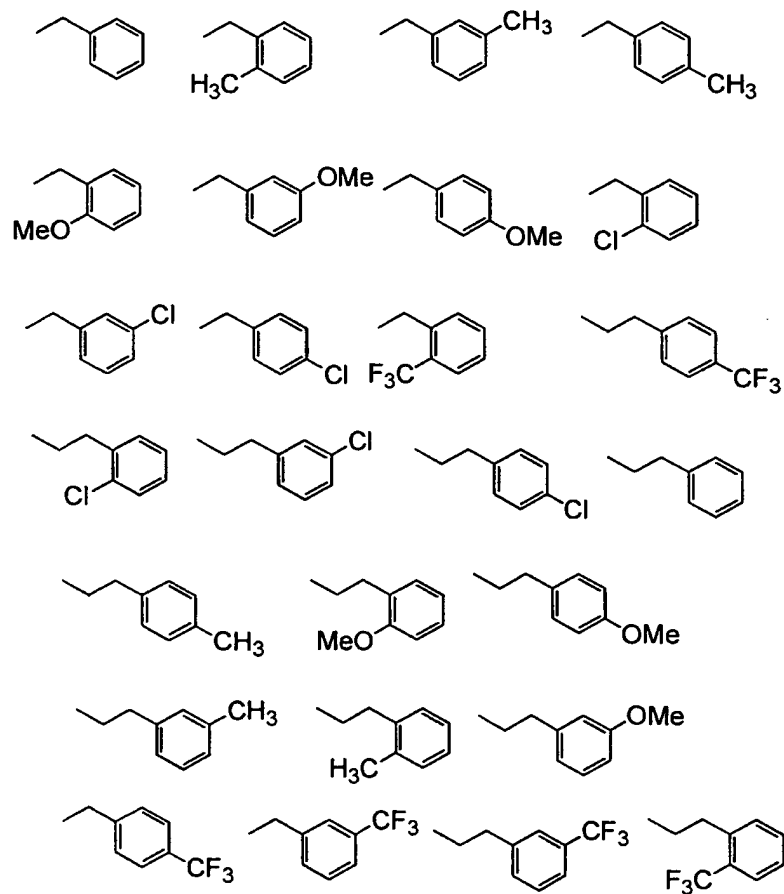
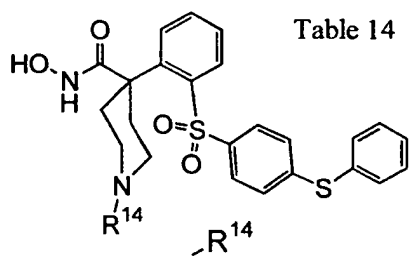


Table 12

Example	X	Example	X
1		8	
2		9	
3		10	
4		11	
5			
6			
7			

Table 13





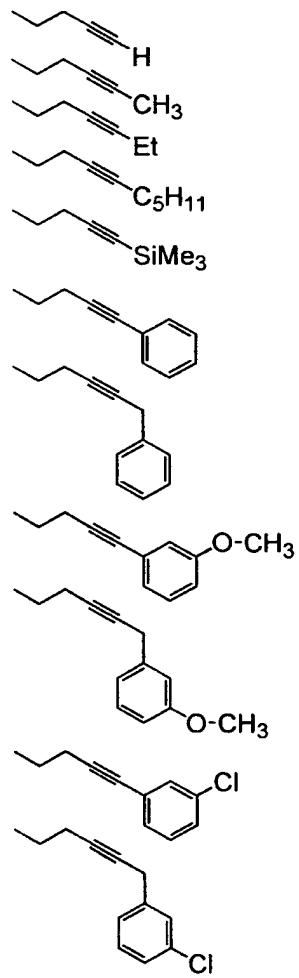
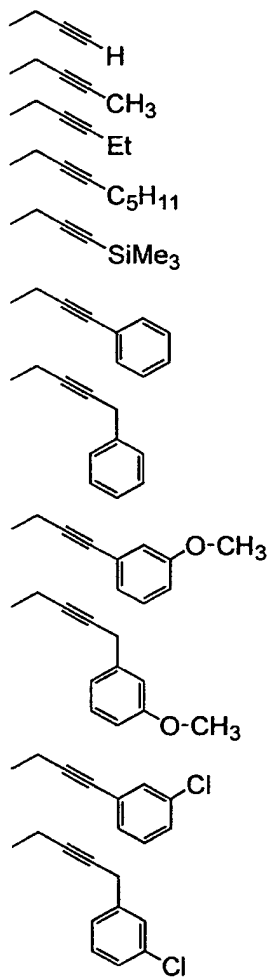
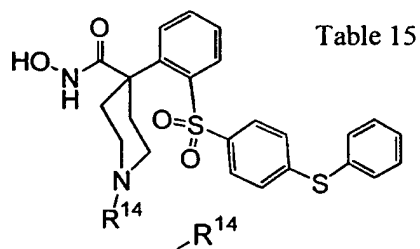
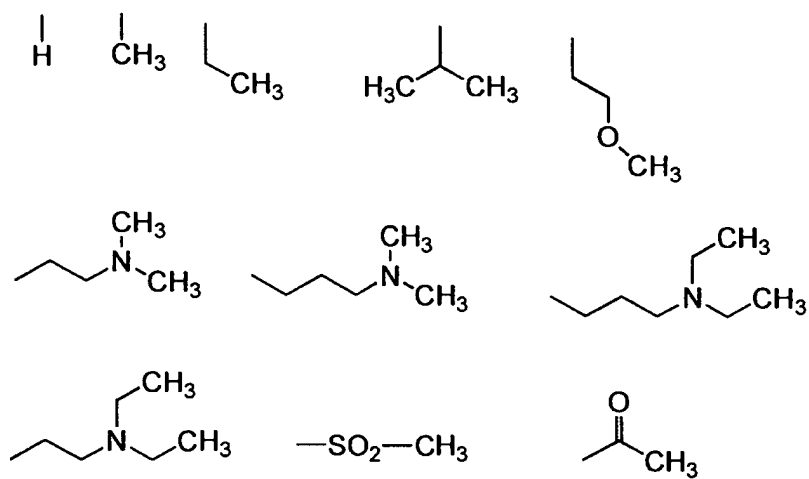
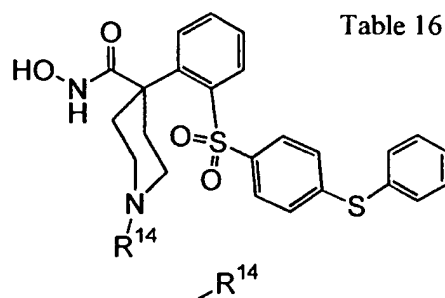


Table 16



5

10

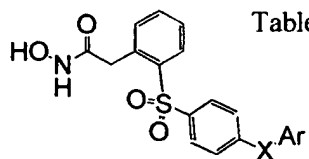


Table 17

Example	X	Ar	Example	X	Ar
1	O		12	S	
2	O		13	S	
3	O		14	S	
4	O		15	S	
5	O		16	S	
6	O		17	S	
7	O		18	S	
8	O		19	S	
9	O		20	S	
10	O		21	S	
11	O		22	S	

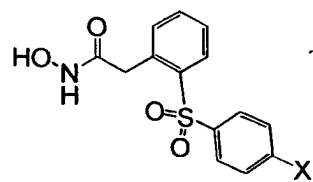
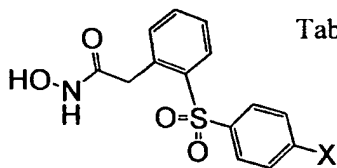


Table 18

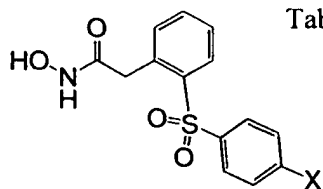
Example	X	Example	X
1		8	
2		9	
3		10	
4		11	
5			
6			
7			

Table 19



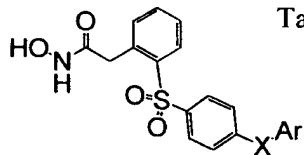
Example	X	Example	X
1		11	
2		12	
3		13	
4		14	
5		15	
6		16	
7		17	
8		18	
9		19	
10		20	

Table 20



Example	X	Example	X
1		9	
2		10	
3		11	
4		12	
5		13	
6		14	
7		15	
8		16	

Table 21



Example	X	Ar	Example	X	Ar
1	O		9	S	
2	O		10	S	
3	O		11	S	
4	O		12	S	
5	O		13	S	
6	O		14	S	
7	O		15	S	
8	O		16	S	

Table 22

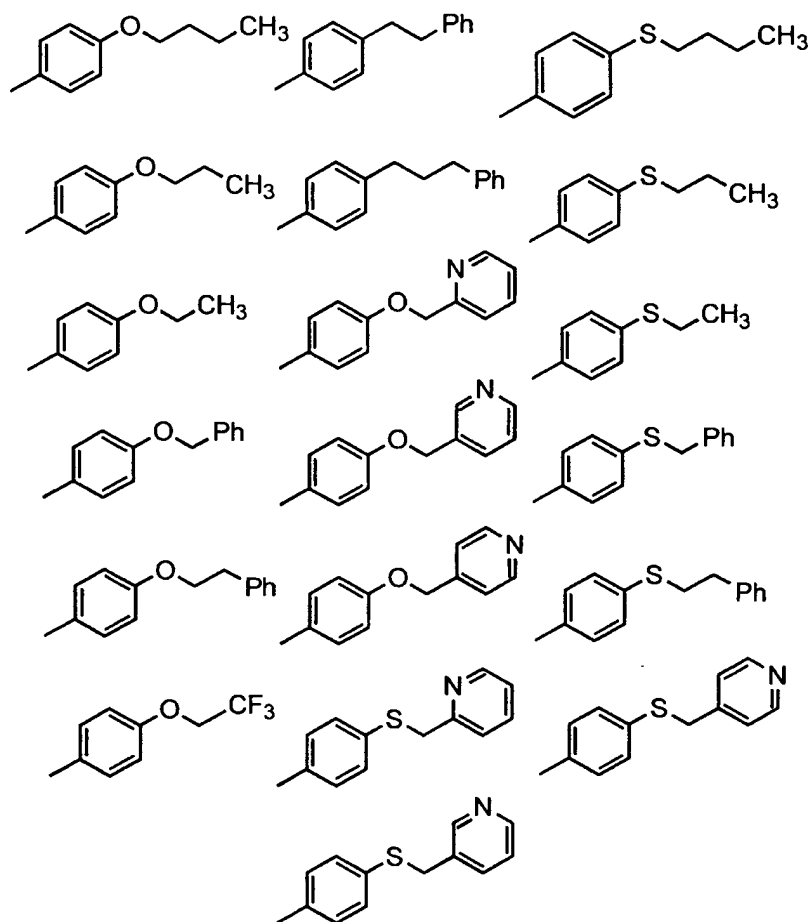
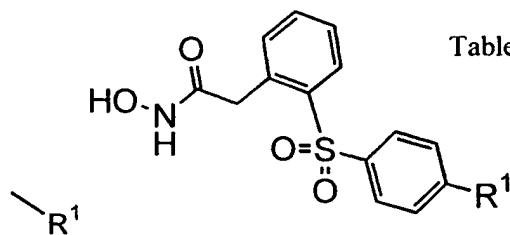
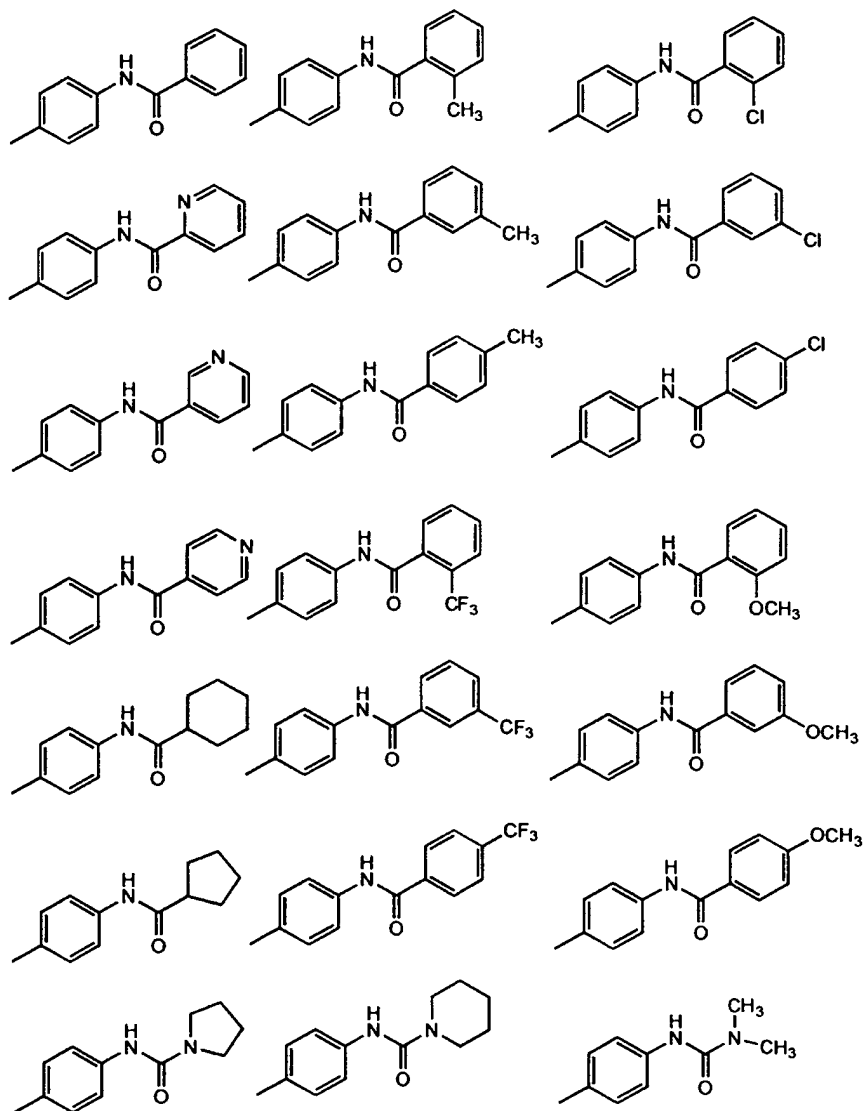
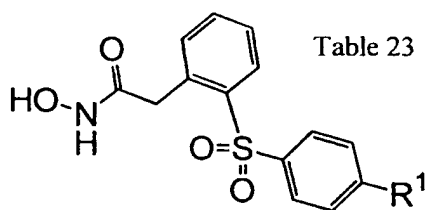


Table 23



5

Table 24

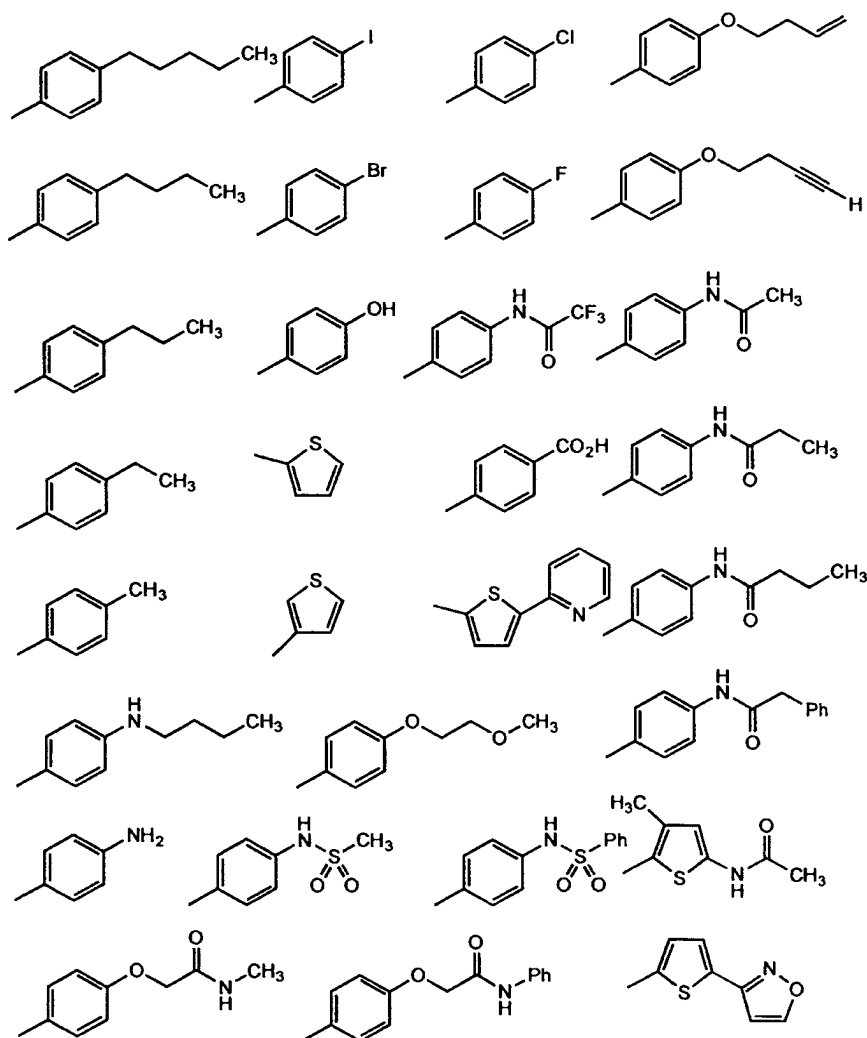
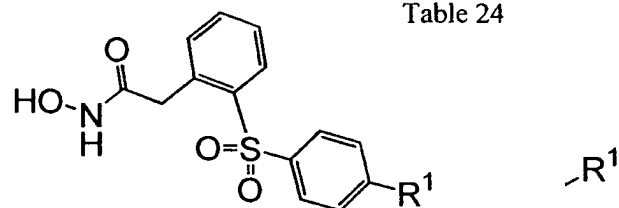


Table 25

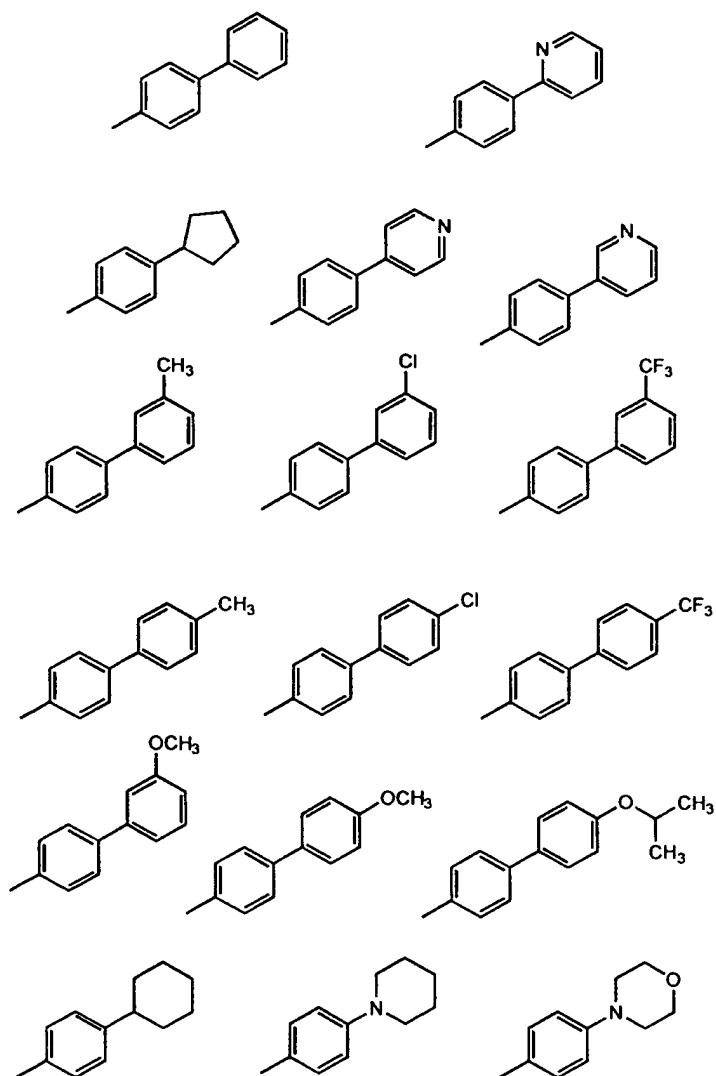
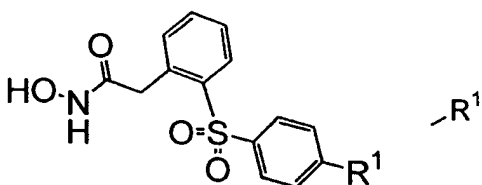


Table 26

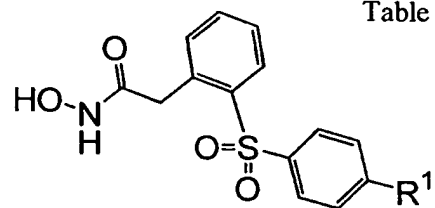
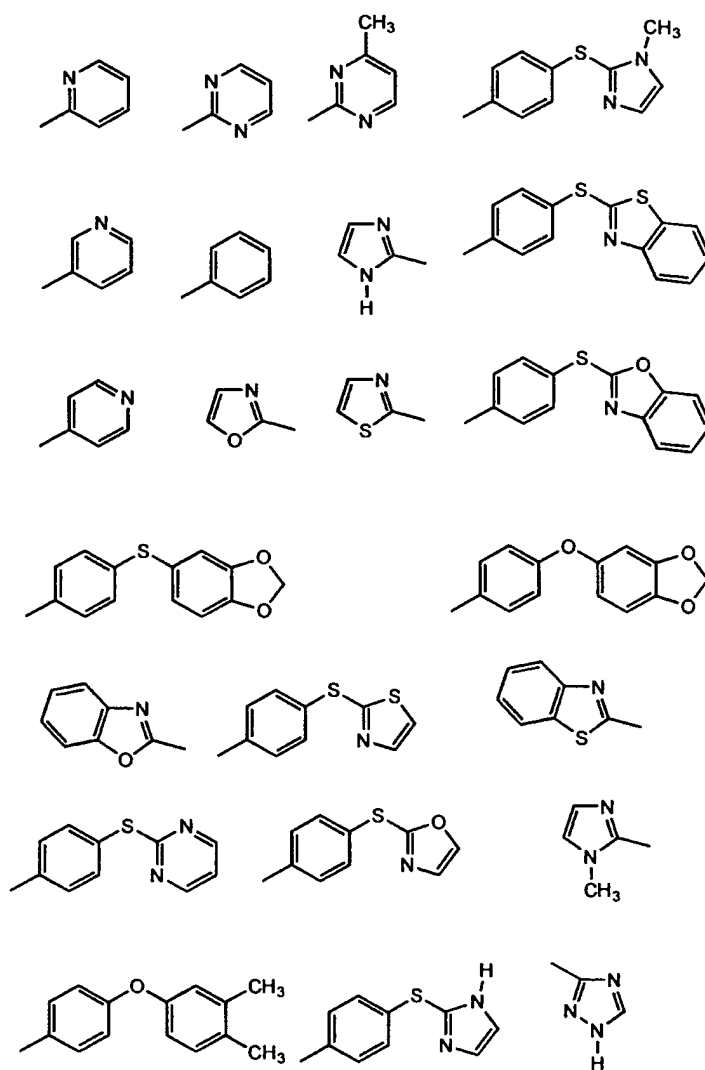
 -R^1 

Table 27

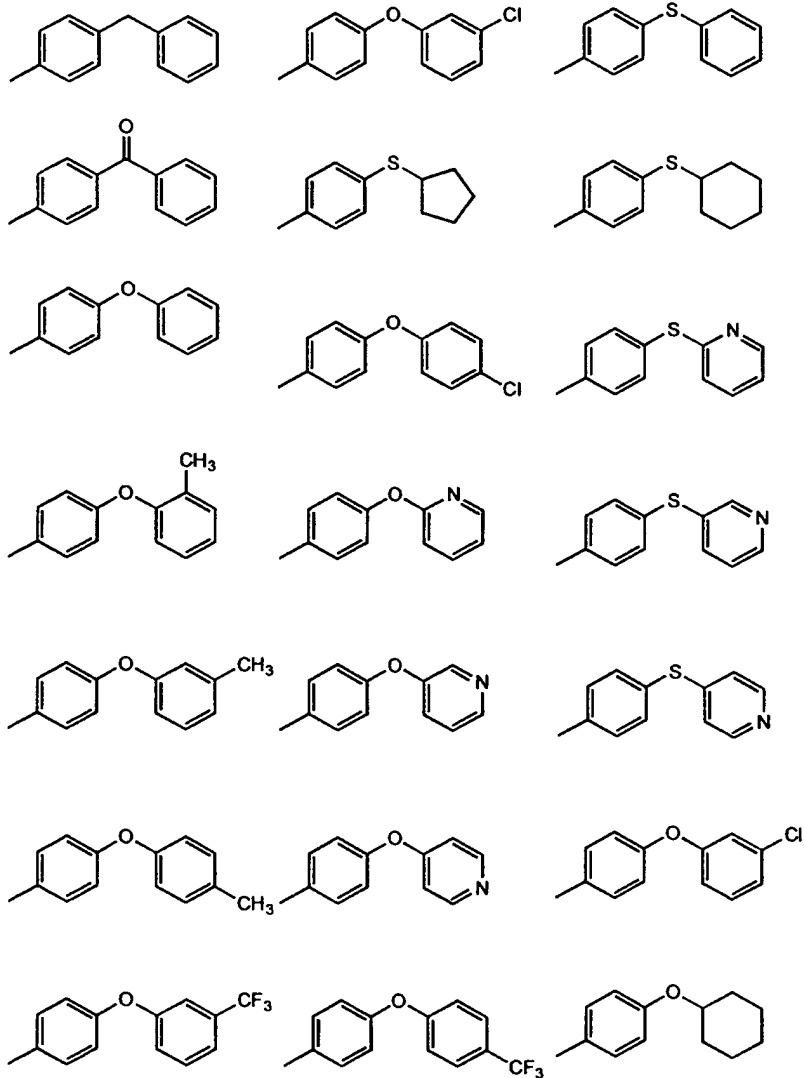
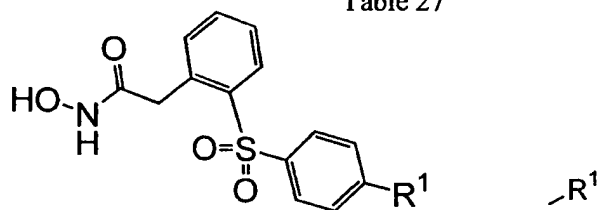


Table 28

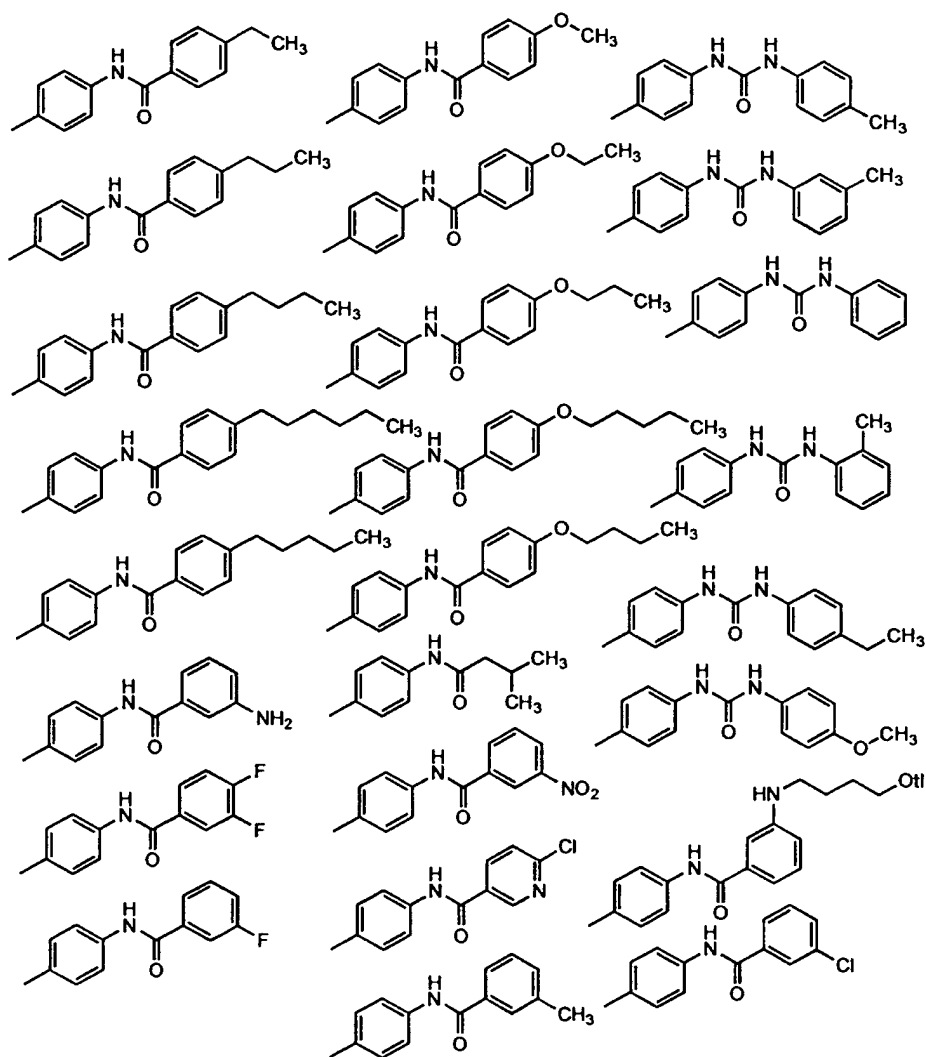
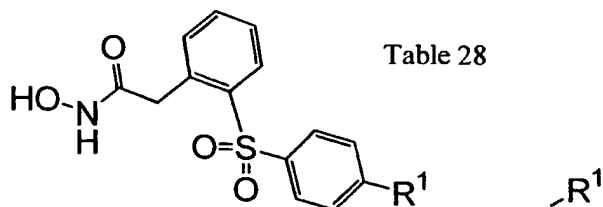
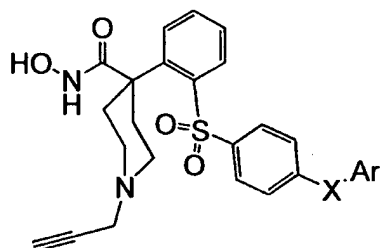


Table 29



Example	X	Ar
1	O	
2	O	
3	S	
4	S	
5	S	
6	S	

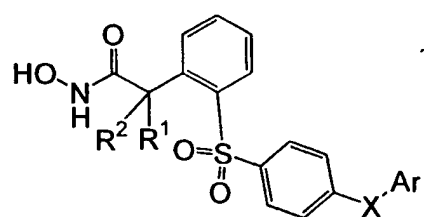
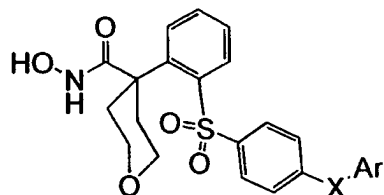


Table 30

Example	R ¹	R ²	X	Ar
1			O	
2			O	
3			O	
4			O	
5			O	
6			O	
7			O	
8			O	
9			S	
10			S	
11			S	

Table 31



Example	X	Ar
1	O	
2	O	
3	S	
4	S	
5	S	

Treatment Process

A process for treating a host mammal having a condition associated with pathological matrix metalloprotease activity is also contemplated. That process comprises administering a compound described hereinbefore in an MMP enzyme-inhibiting effective amount to a mammalian host having such a condition. The use of administration repeated a plurality of times is particularly contemplated.

A contemplated compound is used for treating a host mammal such as a mouse, rat, rabbit, dog, horse, primate such as a monkey, chimpanzee or human that has a condition associated with
5 pathological matrix metalloprotease activity.

Also contemplated is the similar use of a contemplated compound in the treatment of a disease state that can be affected by the activity of metalloproteases such as TNF- α convertase. Exemplary
10 of such disease states are the acute phase responses of shock and sepsis, coagulation responses, hemorrhage and cardiovascular effects, fever and inflammation, anorexia and cachexia.

In treating a disease condition associated
15 with pathological matrix metalloproteinase activity, a contemplated MMP inhibitor compound can be used, where appropriate, in the form of an amine salt derived from an inorganic or organic acid. Exemplary acid salts include but are not limited to the
20 following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate,
25 hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate,
30 picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate and undecanoate.

Also, a basic nitrogen-containing group can be quaternized with such agents as lower alkyl (C₁-

C₆) halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain (C₈-C₂₀) halides such as decyl, lauryl, myristyl and dodecyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others to provide enhanced water-solubility. Water or oil-soluble or dispersible products are thereby obtained as desired. The salts are formed by combining the basic compounds with the desired acid.

Other compounds useful in this invention that are acids can also form salts. Examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases or basic quaternary ammonium salts.

In some cases, the salts can also be used as an aid in the isolation, purification or resolution of the compounds of this invention.

Total daily dose administered to a host mammal in single or divided doses of an MMP enzyme-inhibiting effective amount can be in amounts, for example, of about 0.001 to about 100 mg/kg body weight daily, preferably about 0.001 to about 30 mg/kg body weight daily and more usually about 0.01 to about 10 mg. Dosage unit compositions can contain such amounts or submultiples thereof to make up the daily dose. A suitable dose can be administered, in multiple sub-doses per day. Multiple doses per day can also increase the total daily dose, should such dosing be desired by the person prescribing the drug.

The dosage regimen for treating a disease condition with a compound and/or composition of this

invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration,

5 pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus,

10 the dosage regimen actually employed can vary widely and therefore can deviate from the preferred dosage regimen set forth above.

A compound useful in the present invention can be formulated as a pharmaceutical composition.

15 Such a composition can then be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired.

20 Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal

25 injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania; 1975 and Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980.

30

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using

suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter, synthetic mono- di- or triglycerides, fatty acids and polyethylene glycols that are sold at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration can include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds can be admixed with lactose, sucrose,

starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise

adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the mammalian host treated and the particular mode of administration.

10 Preparation of Useful Compounds

Procedures are provided in the discussion and schemes that follow of exemplary chemical transformations that can be useful for the preparation of compounds of this invention. These syntheses, as with all of the reactions discussed herein, can be carried out under a dry inert atmosphere such as a nitrogen or argon if desired. Selected reactions known to those skilled in the art, can be carried out under a dry atmosphere such as dry air whereas other synthetic steps, for example, aqueous acid or base ester or amide hydrolyses, can be carried out under laboratory air.

Aryl and heteroaryl aryl compounds of this invention as defined above by W can be prepared in a similar manner as is known to those skilled in the art. It should be understood that the discussion below refers to both aromatic systems, i. e., heteroaromatics and carbon aromatics, even though only one may be specifically mentioned.

In general, the choices of starting material and reaction conditions can vary as is well known to those skilled in the art. Usually, no single set of conditions is limiting because variations can be applied as required and selected by one skilled in the art. Conditions will also be selected as desired to suit a specific purpose such as small

scale preparations or large scale preparations. In either case, the use of less safe or less environmentally sound materials or reagents will usually be minimized. Examples of such less desirable materials are diazomethane, diethyl ether, heavy metal salts, dimethyl sulfide, some halogenated solvents, benzene and the like. In addition, many starting materials can be obtained from commercial sources from catalogs or through other arrangements.

10 An aromatic compound of this invention where y is 1 can be prepared as illustrated by converting a carbonyl group bonded to an aromatic (e.g., benzene) ring ortho-substituted with a sulfide. The sulfide can be prepared via a nucleophilic displacement reaction of the ortho fluoride.

15 The nucleophile can be a thiol or thiolate anion prepared from a aryl thiol discussed below. A preferred thiol is 4-phenoxybenzenethiol converted in situ into its anion (thiolate) using potassium carbonate in iso-propyl alcohol at reflux temperature.

20 The carbonyl group can be a aldehyde, ketone or carboxylic acid derivative, i.e, a protected carboxylic acid or hydroxamate. A preferred carbonyl group is an aldehyde and a preferred aldehyde is 2-fluorobenzaldehyde (ortho-fluorobenzaldehyde). A ketone can be converted by oxidation into an acid and/or an acid derivative using reagents such as those discussed below for oxidation of a sulfide or other methods well known in the art. It is noted that this oxidation can accomplish the oxidation of a sulfide intermediate into the corresponding sulfone in the same reaction system; i.e., in the same pot, if desired.

35 The carbonyl group can then be homologated if desired by reaction with an anion to form an addition compound. An example of a homologation

reagent is a tri-substituted methane compound such as tetraethyl dimethylammoniummethylenediphosphonate or trimethylorthoformate. Tetraethyl dimethylammoniummethylenediphosphonate is preferred.

5 Hydrolysis of the reaction product can provide a phenylacetic substituted on the aromatic ring with a sulfide of this invention. Acid hydrolysis is preferred. Acids and bases are discussed below and hydrochloric acid is preferred.

10 The sulfide can then be oxidized to form a sulfone in one or two steps as discussed below. A preferred oxidizing agent is hydrogen peroxide in acetic acid. The carboxylic acid product or intermediate of this invention can then be converted
15 into a protected derivative such as an ester or converted into an activated carboxyl group for reaction with hydroxylamine or and protected hydroxylamine; i.e, a hydroxamate. The conversion of an acid into a hydroxamate is discussed below as is
20 the coupling process and removal of a protecting group if required.

The preferred protected hydroxamic acid derivative is the O-tetrahydropyranyl compound and the preferred coupling procedure utilizes a diimide
25 (EDC), hydroxybenzotriazol and DMF solvent for the coupling reaction to form the intermediate hydroxybenzotriazol activated ester. A preferred reagent for removal of the THP protecting group is hydrochloric acid.

30 Alkylation of the acid at the carbon alpha to the carbonyl group to form the compounds of this invention can be carried out by first forming an anion using a base. Bases are discussed below. The preferred bases are strong bases that are either
35 hindered and/or non-nucleophilic such as lithium amides, metal hydrides or lithium alkyls.

Following or during formation of the anion, an alkylating agent (an electrophile) is added that undergoes a nucleophilic substitution reaction. Non-limiting examples of such alkylating agents are haloalkanes, dihaloalkanes, haloalkanes also substituted by an activated ester group or activated esters and alkanes substituted with sulfate esters.

Activated ester groups are well known in the art and can include, for example, an activated ester of an alcohol or a halo compound, an ester of a haloalcohol such as a bromo-, iodo- or chloro-derivative of a tosylate, triflate or mesylate activated ester. Compounds wherein, for example, R^2 and R^3 are taken together as defined above, can be prepared using disubstituted alkylating agent; i.e., alkylating agents with two leaving groups in the same molecule. For example, 1,5-dihalo-diethylether or analogous reagents containing one or more sulfate ester leaving groups replacing one or more halogens can be used to form a pyran ring. A similar sulfur, nitrogen or protected nitrogen alkylating agent can be used to form a thiapyran or piperidine ring. A thiapyran can be oxidized to form a sulfoxide or a sulfone using methods discussed herein. A leaving group in an electrophilic reagent, as is well known in the art, can be a halogen such as chlorine, bromine or iodine or an active ester such as a sulfonate ester, e.g., toluenesulfonate (tosylate), triflate, mesylate and the like as discussed above.

The conversion of a cyclic amino acid, heterocycle or alpha-amino acid defined by R^2 and R^3 that can include an amino acid (nitrogen heterocycle), which can be protected or unprotected, into a compound of this invention can be accomplished by alkylation or acylation. The carboxylic acid group can be protected with a group such as an alkyl ester such as methyl, ethyl, tert-butyl and the like

or a tetrahydropyranyl ester or an arylalkyl ester such as benzyl or it can remain as a carboxylic acid. A protected amino acid such as an ethyl ester is preferred. The substituent on the heterocycle group is as defined above and can include hydrogen, tert-butoxycarbonyl (BOC or tBOC), benzyloxycarbonyl (Z) and iso-butyloxycarbonyl groups. In addition, the amine can be considered as being a protected intermediate as well as being a product of this invention when the N-substituent is not hydrogen.

The nitrogen substituent on the amino acid portion of the compounds of this invention can be varied. In addition, that variation can be accomplished at different stages in the synthetic sequence based on the needs and objectives of the skilled person preparing the compounds of this invention. The nitrogen side chain variations can include replacing the hydrogen substituent with a alkyl, arylalkyl, alkene or alkyne.

This can be accomplished by methods well known in the art such as alkylation of the amine with an electrophile such as halo- or sulfate ester (activated ester) derivative of the desired sidechain. An alkylation reaction is typically carried out in the presence of a base such as those discussed above and in a pure or mixed solvent as discussed above. A preferred base is potassium carbonate and a preferred solvent is DMF.

The alkenes, arylalkenes, arylalkynes and alkynes so formed can be reduced, for example, by hydrogenation with a metal catalyst and hydrogen, to an alkyl or arylalkyl compound of this invention and a alkyne or arylalkyne can be reduced to a alkene, arylalkene, arylalkane or alkane with under catalytic hydrogenation conditions as discussed herein or with an deactivated metal catalyst. Catalysts can include, for example, Pd, Pd on Carbon, Pt, PtO₂ and

the like. Less robust catalysts (deactivated) include such thing as Pd on BaCO₃ or Pd with quinoline or/and sulfur.

5 An alternative method for alkylation of the amine nitrogen is reductive alkylation. This process, well known in the art, allows treatment of the secondary amine with an aldehyde or ketone in the presence of a reducing agent such as borane, borane:THF, borane:pyridine, lithium aluminum
10 hydride. Alternatively, reductive alkylation can be carried out under hydrogenation conditions in the presence of a metal catalyst. Catalysts, hydrogen pressures and temperatures are discussed and are well known in the art. A preferred reductive alkylation
15 catalyst is borane:pyridine complex.

In the case where an intermediate is a carboxylic acid, standard coupling reactions well known in the art can be used to form the compounds of this invention including protected intermediates.
20 For example, the acid can be converted into an acid chloride, mixed anhydride or activated ester and reacted with an alcohol, amine, hydroxylamine or a protected hydroxylamine in the presence of base to form the amide, ester, hydroxamic acid, protected
25 hydroxamic acid. This is the same product as discussed above. Bases are discussed above and include N-methyl-morpholine, triethylamine and the like.

Coupling reactions of this nature are well
30 known in the art and especially the art related to peptide and amino acid chemistry. Removal of the protecting group can be accomplished, if desired, using standard hydrolysis conditions such as base hydrolysis or exchange or acid exchange or hydrolysis
35 as discussed.

The Schemes and/or dicussion also illustrate conversion of a carboxylic acid protected

as an ester or amide into an hydroxamic acid derivative such as a O-arylalkylether or O-cycloalkoxyalkylether group such as the THP group. Methods of treating an acid or acid derivative with

5 hydroxylamine or a hydroxylamine derivative to form a hydroxamic acid or hydroxamate derivative are discussed above. Hydroxylamine can be used in an exchange reaction by treatment of a precursor compound where the carboxyl is protected as an ester

10 or amide with one or more equivalents of hydroxylamine hydrochloride or hydroxylamine at room temperature or above to provide a hydroxamic acid directly. The solvent or solvents, usually protic or protic solvent mixtures such as those listed herein.

15 This exchange process can be further catalyzed by the addition of additional acid. Alternatively, a base such as a salt of an alcohol used as a solvent, for example, sodium methoxide in methanol, can be used to form hydroxylamine from

20 hydroxylamine hydrochloride in situ which can exchange with an ester or amide. As mentioned above, exchange can be carried out with a protected hydroxylamine such as tetrahydropyranyl-hydroxylamine (THPONH₂), benzylhydroxylamine (BnONH₂), O-

25 (trimethylsilyl)hydroxylamine and the like, in which case the compounds formed are tetrahydropyranyl (THP), benzyl (Bn) or TMS hydroxamic acid derivatives. Removal of the protecting groups when desired, for example, following further

30 transformations in another part of the molecule or following storage, can be accomplished by standard methods well known in the art such as acid hydrolysis of the THP group as discussed above or reductive removal of the benzyl group with hydrogen and a metal

35 catalyst such as palladium, platinum, palladium on carbon or nickel.

alpha-Amino acids or alpha-hydroxy carboxylic acids or protected carboxylic acids, hydroxamates or hydroxamic acid derivatives or intermediates (precursors) of this invention can be prepared by displacing, for example, a halogen, sulfate ester or other electrophile, from the alpha carbon of an acid or a derivative as listed. Methods for the halogenation of acids, esters, acid chlorides and like are well known in the art and include, for example, the HVZ reaction, treatment with CuCl_2 , N-bromo- or N-chloro-succinimide, I_2 , carbon tetraiodide or bromide and the like. The halogen can be displaced with a nucleophile in an SN_2 reaction. Nucleophiles can include hydroxide, ammonia or amines.

The aryl or heteroaryl carboxylic acids of this invention where Y is 0 and z is 1 can be prepared from heteroaryl or aryl fused lactones. An example of a fused lactone is phthalide. A preferred starting material is phthalide. This compound can be treated with an thiol, thiolate or metal -SH in order to undergo a SN_2 displacement at the methylene carbon to provide a sulfide or thiol compound of this invention or intermediate to a compound of this invention. A preferred thiol is 4-phenoxybenzenethiol that is used in the presence of potassium carbonate as a preferred base. The sulfide can be oxidized, before or after conversion of the acid to a hydroxamate or hydroxamic acid, to a sulfone of this invention. A preferred oxidizing agent is meta-chloroperbenzoic acid.

A preferred acid activating group is the chloride prepared by reaction of an acid with oxalyl chloride as a preferred reagent. A phthalide or a heteroaryl analog of a phthalide can be treated with a Lewis acid such as zinc chloride or zinc bromide along with a halogenating reagent such as phosphorus

trichloride or thionyl bromide or the like to form a ortho-(haloalkyl)-aryl acid or ortho-(haloalkyl)-heteroaryl acid derivative. Examples include bromomethyl acid bromides and chloromethyl acid chlorides. These carboxylic acids can be derivatized with protecting groups, hydroxamic acids or hydroxamic acid precursors (hydroxamates) or hydrolyzed to the acid as required. A preferred hydroxamate forming reagent is O-(trimethylsilyl)hydroxylamine (TMS-hydroxylamine) and removal of the TMS protecting group is preferably accomplished by acid hydrolysis using hydrochloric acid.

Displacement (SN_2) of the halogen in this example by a thiol in the presence of base or a preformed thiolate can be accomplished as discussed and/or shown and as is well known in the art. Again, oxidation of the sulfide can be carried out before or after derivatization of the carboxylic acid as discussed to prepare the hydroxamic acids of this invention. Removal of the protecting groups can be carried out using acid hydrolysis or reduction as discussed elsewhere in this document.

The alcohols of this invention can be protected or deprotected as required or desired. Protecting groups can include THP ethers, acylated compounds and various silyl derivatives. These groups, including their protection and removal, are well known in the art.

Examples of bases that can be used include, for example, metal hydroxides such as sodium, potassium, lithium or magnesium hydroxide, oxides such as those of sodium, potassium, lithium, calcium or magnesium, metal carbonates such as those of sodium, potassium, lithium, calcium or magnesium, metal bicarbonates such as sodium bicarbonate or potassium bicarbonate, primary (I°), secondary (II°)

or tertiary (III°) organic amines such as alkyl amines, arylalkyl amines, alkylarylalkyl amines, heterocyclic amines or heteroaryl amines, ammonium hydroxides or quaternary ammonium hydroxides. As
5 non-limiting examples, such amines can include triethyl amine, trimethyl amine, diisopropyl amine, methyldiisopropyl amine, diazabicyclononane, tribenzyl amine, dimethylbenzyl amine, morpholine, N-methylmorpholine, N,N'-dimethylpiperazine, N-ethylpiperidine, 1,1,5,5-tetramethylpiperidine,
10 dimethylaminopyridine, pyridine, quinoline, tetramethylethylenediamine and the like.

Non-limiting examples of ammonium hydroxides, usually made from amines and water, can
15 include ammonium hydroxide, triethyl ammonium hydroxide, trimethyl ammonium hydroxide, methyldiisopropyl ammonium hydroxide, tribenzyl ammonium hydroxide, dimethylbenzyl ammonium hydroxide, morpholinium hydroxide, N-methylmorpholinium hydroxide, N,N'-
20 dimethylpiperazinium hydroxide, N-ethylpiperidinium hydroxide, and the like. As non-limiting examples, quaternary ammonium hydroxides can include tetraethyl ammonium hydroxide, tetramethyl ammonium hydroxide, dimethyldiisopropyl ammonium hydroxide,
25 benzylmethyldiisopropyl ammonium hydroxide, methyldiazabicyclononyl ammonium hydroxide, methyltribenzyl ammonium hydroxide, N,N'-dimethylmorpholinium hydroxide, N,N,N', N',-tetramethylpiperazinium hydroxide, and N-ethyl-N'-
30 hexylpiperidinium hydroxide and the like. Metal hydrides, amide or alcoholates such as calcium hydride, sodium hydride, potassium hydride, lithium hydride, sodium methoxide, potassium tert-butoxide,
35 calcium ethoxide, magnesium ethoxide, sodium amide, potassium diisopropyl amide and the like can also be suitable reagents. Organometallic deprotonating

agents such as alkyl or aryl lithium reagents such as methyl, phenyl, butyl, iso-butyl, sec-butyl or tert-butyl lithium, sodium or potassium salts of dimethylsulfoxide, Grignard reagents such as
5 methylmagnesium bromide or methymagnesium chloride, organocadmium reagents such as dimethylcadmium and the like can also serve as bases for causing salt formation or catalyzing the reaction. Quaternary ammonium hydroxides or mixed salts are also useful
10 for aiding phase transfer couplings or serving as phase transfer reagents. Preferred base for use in the alkylation reaction is lithium diisopropyl amide as mentioned above.

Reaction media in general can be comprised
15 of a single solvent, mixed solvents of the same or different classes or serve as a reagent in a single or mixed solvent system. The solvents can be protic, non-protic or dipolar aprotic. Non-limiting examples of protic solvents include water, methanol (MeOH),
20 denatured or pure 95% or absolute ethanol, isopropanol and the like.

Typical non-protic solvents include acetone, tetrahydrofuran (THF), dioxane, diethylether, tert-butylmethyl ether (TBME),
25 aromatics such as xylene, toluene, or benzene, ethyl acetate, methyl acetate, butyl acetate, trichloroethane, methylene chloride, ethylenedichloride (EDC), hexane, heptane, isooctane, cyclohexane and the like. Dipolar aprotic solvents
30 include compounds such as dimethylformamide (DMF), dimethylacetamide (DMAc), acetonitrile, nitromethane, tetramethylurea, N-methylpyrrolidone and the like.

Non-limiting examples of reagents that can be used as solvents or as part of a mixed solvent
35 system include organic or inorganic mono- or multi-protic acids or bases such as hydrochloric acid, phosphoric acid, sulfuric acid, acetic acid, formic

acid, citric acid, succinic acid, triethylamine, morpholine, N-methylmorpholine, piperidine, pyrazine, piperazine, pyridine, potassium hydroxide, sodium hydroxide, alcohols or amines for making esters or amides or thiols for making the products of this invention and the like. Room temperature or less or moderate warming (-10°C to 60°C) are the preferred temperatures of the reaction. If desired, the reaction temperature might be about -78°C to the reflux point of the reaction solvent or solvents. The preferred solvent for an alkylation reaction is tetrahydrofuran (THF).

Acids are used in many reactions during various synthesis. The Schemes as well as this discussion preparative methods illustrate acid use for the removal of the THP protecting group to produce a hydroxamic acid, removal of a tert-butoxy carbonyl group, hydroxylamine/ester exchange and the like. Acid hydrolysis of carboxylic acid protecting groups or derivatives is well known in the art. These methods, as is well known in the art, can use acid or acidic catalysts. The acid can be mono-, di- or tri-protic organic or inorganic acids. Examples of acids include hydrochloric acid, phosphoric acid, sulfuric acid, acetic acid, formic acid, citric acid, succinic acid, hydrobromic acid, hydrofluoric acid, carbonic acid, phosphorus acid, p-toluene sulfonic acid, trifluoromethane sulfonic acid, trifluoroacetic acid, difluoroacetic acid, benzoic acid, methane sulfonic acid, benzene sulfonic acid, 2,6-dimethylbenzene sulfonic acid, trichloroacetic acid, nitrobenzoic acid, dinitrobenzoic acid, trinitrobenzoic acid, and the like. They can also be Lewis acids such as aluminum chloride, borontrifluoride, antimony pentafluoride and the like.

Contemplated compounds can include compounds wherein a nitrogen of an amine is acylated to provide, for example, amino acid carbamates. Non-limiting examples of these carbamates are the carbobenzoxycarbonyl (Z, CBZ, benzyloxycarbonyl), iso-butoxycarbonyl and tert-butoxycarbonyl (BOC, t-BOC) compounds. The materials can be made, as discussed above, at various stages in the synthesis based on the needs and decisions made by a person skilled in the art using methods well known in the art.

Useful synthetic techniques and reagents include those used in protein, peptide and amino acid synthesis, coupling and transformation chemistry. The use of the tert-butoxycarbonyl (BOC) and benzyloxycarbonyl (Z) as well as their synthesis and removal are examples of such protection or synthesis schemes. Transformations of amino acids, amino esters, amino acid hydroxamates, amino acid hydroxamate derivatives and amino acid amides of this invention or compounds used in this invention is discussed herein or/and shown in the schemes. This includes, for example, active ester or mixed anhydride couplings wherein preferred bases, if required, are tertiary amines such as N-methylmorpholine. Reagents for protection of the amine group of the protected amino acids include carbobenzoxy chloride, iso-butylchloroformate, tert-butoxycarbonyl chloride, di-tert-butyl dicarbonate and the like which are reacted with the amine in non-protic or dipolar aprotic solvents such as DMF or THF or mixtures of solvents.

Removal of protecting groups such as carbamates, silyl groups and benzyl, p-methoxybenzyl, or other substituted benzyl groups or diphenylmethyl (benzhydryl) or triphenylmethyl (trityl) can be carried out at different stages in the synthesis of

the compounds of this invention as required by methods selected by one skilled in the art. These methods are well known in the art including the amino acid, amino acid coupling, peptide synthesis, peptide mimetic synthesis art. Removal methods can include catalytic hydrogenation, base hydrolysis, carbonyl addition reactions, acid hydrolysis and the like. Both the preparation and removal of protecting groups, for example, carbamates, benzyl groups and/or substituted arylalkyl groups is discussed in Green, T., Protecting Groups in Organic Chemistry, Second ed., John Wiley & Sons, New York (1991). A preferred method of removal of a BOC group is HCl gas in methylene chloride which, following normal workup, provides directly an HCl salt of an aminoacid of this invention.

Sulfone compounds such as those where R^1 is nitrobenzene can be prepared as compounds of this invention by synthesis of a thiol, displacement of an electrophile by the nucleophilic thiol or thiolate and oxidation of the product thiol ether to the sulfone. For example, displacement of the electrophilic group with a nitro-benzene thiol can yield a compound where R^1 is nitrobenzene, whose nitro group can be reduced to provide a useful amino compound wherein R^1 is an aniline. It should be noted that nitrobenzenethiol is an example and not to be considered as limiting or required. Oxidation of the thioether product can be carried out as discussed below when desired.

The reduction of nitro groups to amines is well known in the art with a preferred method being hydrogenation. There is usually a metal catalyst such as Rh, Pd, Pt, Ni or the like with or without an additional support such as carbon, barium carbonate and the like. Solvents can be protic or non-protic pure solvents or mixed solvents as required. The

reductions can be carried out at atmospheric pressure to a pressure of multiple atmospheres with atmospheric pressure to about 40 pounds per square inch (psi) preferred.

5 The resulting amino group can be alkylated if desired. It can also be acylated with, for example, an aroyl chloride, heteroaryl chloride or other amine carbonyl forming agent to form an R¹ amide of this invention. The amino sulfone or
10 thioether can also be reacted with a carbonic acid ester chloride, a sulfonyl chloride, a carbamoyl chloride or an isocyanate to produce the corresponding carbamate, sulfonamides, or ureas of this invention. Acylation of amines of this type are
15 well known in the art and the reagents are also well known.

 Usually these reactions are carried out in aprotic solvents under an inert or/and dry atmosphere at about 45°C to about -10°C. An equivalent of a
20 non-competitive base is usually used with sulfonyl chloride, acid chloride or carbonyl chloride reagents. Following or before this acylation step, synthesis of the hydroxamic acid products of this invention can proceed as discussed.

25 Other thiol reagents can also be used in the preparation of compounds of this invention. Examples are fluoroaryl, fluoroheteroaryl, azidoaryl or azidoheteroaryl or heteroaryl thiol reagents. These thiols can be used as nucleophiles to as
30 discussed above. Oxidation to the corresponding sulfone can then be carried out.

 The sulfones, if substituted by a hydrazine or substituted hydrazine, can be oxidized to a hydrazone of this invention. The fluoro substituted
35 sulfone can be treated with a nucleophile such as ammonia, a primary amine, a quaternary ammonium or metal azide salt or a hydrazine under pressure if

desired, to provide an azido, amino, substituted amino or hydrazino group. Azides can be reduced to an amino group using, for example, hydrogen with a metal catalyst or metal chelate catalyst or by an
5 activated hydride transfer reagent. The amines can be acylated as discussed above.

Methods of preparing useful aminethiol intermediates include protection of an aromatic or heteroaromatic thiol with trityl chloride to form the
10 trityl thiol derivative, treatment of the amine with as reagent such as an aromatic or heteroaromatic acid chloride to form the amide, removal of the trityl group, with acid to form the thiol. Acylating agents include benzoyl chloride and trityl removing reagents
15 include trifluoroacetic acid and trisopropylsilane.

The fluorine on the fluorosulfones of this invention can also be displaced with other aryl or heteroaryl nucleophiles for form compounds of this invention. Examples of such nucleophiles include
20 salts of phenols, thiophenols, -OH group containing aromatic heterocyclic compounds or -SH containing heteroaryl compounds. Tautomers of such groups azo, hydrazo, -OH or -SH are specifically included as useful isomers.

25 A preferred method of preparing intermediates in the synthesis of the substituted sulfones is by oxidation of an appropriate acetophenone, prepared from a fluoroacetophenone, with for example, peroxymonosulfate, to form the
30 corresponding phenol-ether. The phenol-ether is converted into its dimethylthiocarbamoyl derivative using dimethylthiocarbamoyl chloride, rearranged into the dimethylthiocarbamoyl derivative with heat to provide the thiol required for preparation of the
35 thioether intermediate discussed and/or shown in the schemes.

The compounds of this invention including protected compounds or intermediates can be oxidized to the sulfones as shown in the schemes and/or discussed above. The selection of the stage of the alternative synthesis to implement this conversion of sulfides into the sulfones or sulfoxides can be carried out by one skilled in the art.

Reagents for this oxidation process may, in a non-limiting example, include peroxymonosulfate (OXONE[®]), hydrogen peroxide, meta-chloroperbenzoic acid, perbenzoic acid, peracetic acid, perlactic acid, tert-butyl peroxide, tert-butyl hydroperoxide, tert-butyl hypochlorite, sodium hypochlorite, hypochlorous acid, sodium meta-periodate, periodic acid, ozone and the like. Protic, non-protic, dipolar aprotic solvents, either pure or mixed, can be chosen, for example, methanol/water. The oxidation can be carried out at temperature of about -78° to about 50° degrees centigrade and normally selected from a range -10°C to about 40°C.

Preparation of the sulfones can also be carried out in two steps by the oxidation of a sulfide to a sulfoxide followed by oxidation of the sulfoxide to the sulfone. This can occur in one pot or by isolation of the sulfoxide. This latter oxidation can be carried out in a manner similar to the oxidation directly to the sulfone except that about one equivalent of oxidizing agent can be used preferably at a lower temperature such as about 0°C. Preferred oxidizing agents include peroxymonosulfate and meta-chloroperbenzoic acid.

Salts of the compounds or intermediates of this invention are prepared in the normal manner wherein acidic compounds are reacted with bases such as those discussed above to produce metal or nitrogen containing cation salts. Basic compounds such as

amines can be treated with an acid to form an amine salt.

Compounds of the present can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes well known in the art, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base.

Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers.

Still another available method involves synthesis of covalent diastereoisomeric molecules, e.g., esters, amides, acetals, ketals, and the like, by reacting compounds of Formula I with an optically active acid in an activated form, a optically active diol or an optically active isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. In some cases hydrolysis to the parent optically active drug is not necessary prior to dosing the patient since the compound can behave as a prodrug. The optically active compounds of Formula I can likewise be obtained by utilizing optically active starting materials.

In addition to the optical isomers or potentially optical isomers discussed above, other types of isomers are specifically intended to be included in this discussion and in this invention. Examples
5 include cis isomers, trans isomers, E isomers, Z isomers, syn- isomers, anti- isomers, tautomers and the like. Aryl, heterocyclo or heteroaryl tautomers, heteroatom isomers and ortho, meta or para substitution isomers are also included as isomers.
10 Solvates or solvent addition compounds such as hydrates or alcoholates are also specifically included both as chemicals of this invention and in, for example, formulations or pharmaceutical compositions for drug delivery.

15 Where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position, e.g., a hydrocarbyl radical or a halogen, hydroxy, amino and the like functional group, is not
20 critical so long as it does not adversely affect the overall activity and/or synthesis procedure. For example, two hydroxyl groups, two amino groups, two thiol groups or a mixture of two hydrogen-heteroatom groups on the same carbon are known not to be stable
25 without protection or as a derivative.

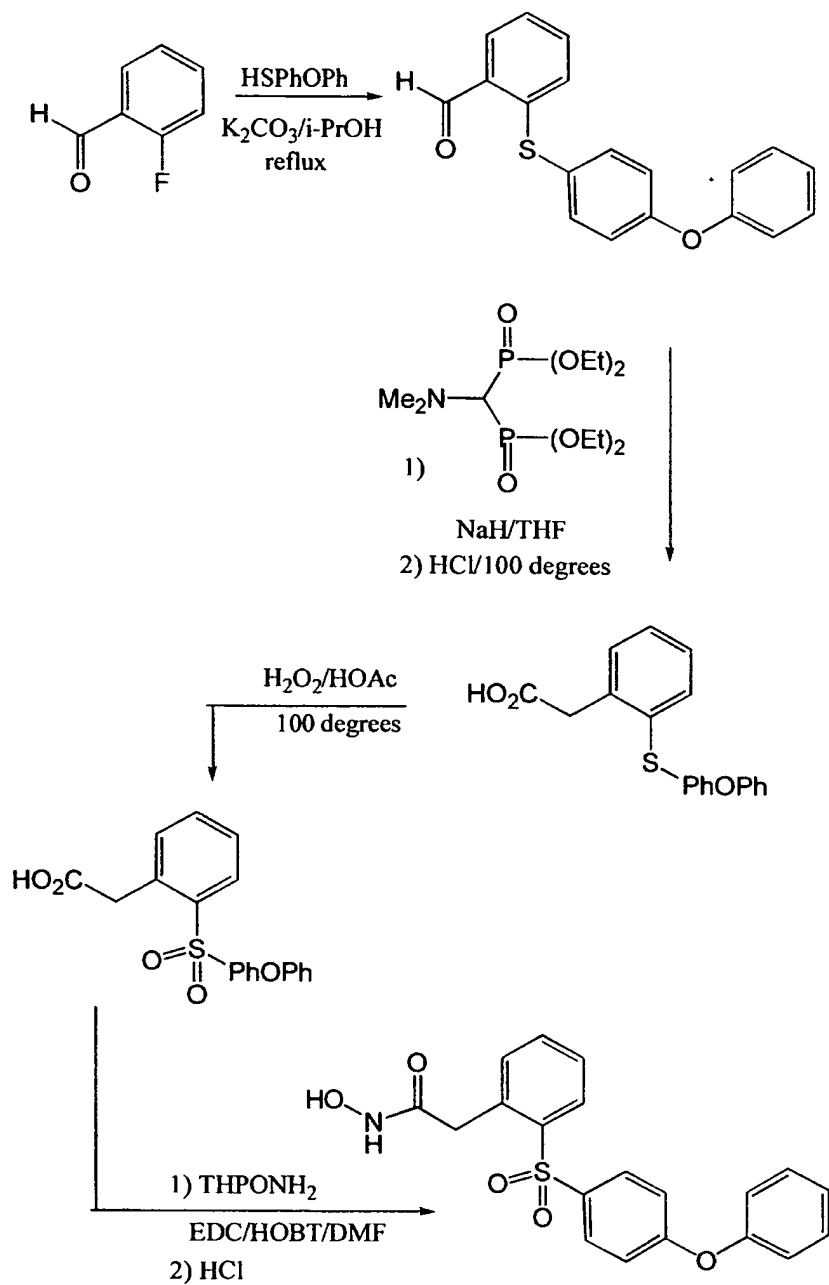
The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions can not
30 be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by
35 conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative

conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding
5 compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

Other compounds of this invention that are acids can also form salts. Examples include salts
10 with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases or basic quaternary ammonium salts.

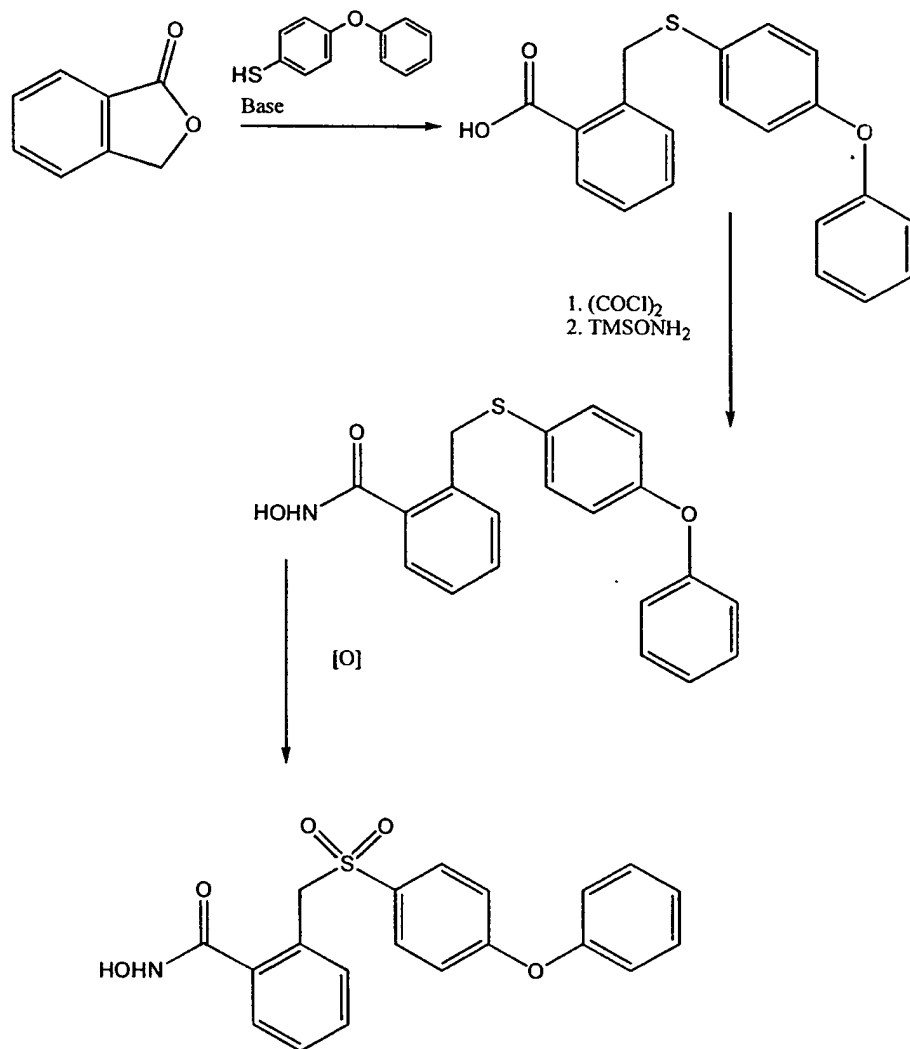
In some cases, the salts can also be used as an aid in the isolation, purification or
15 resolution of the compounds of this invention.

Scheme 1



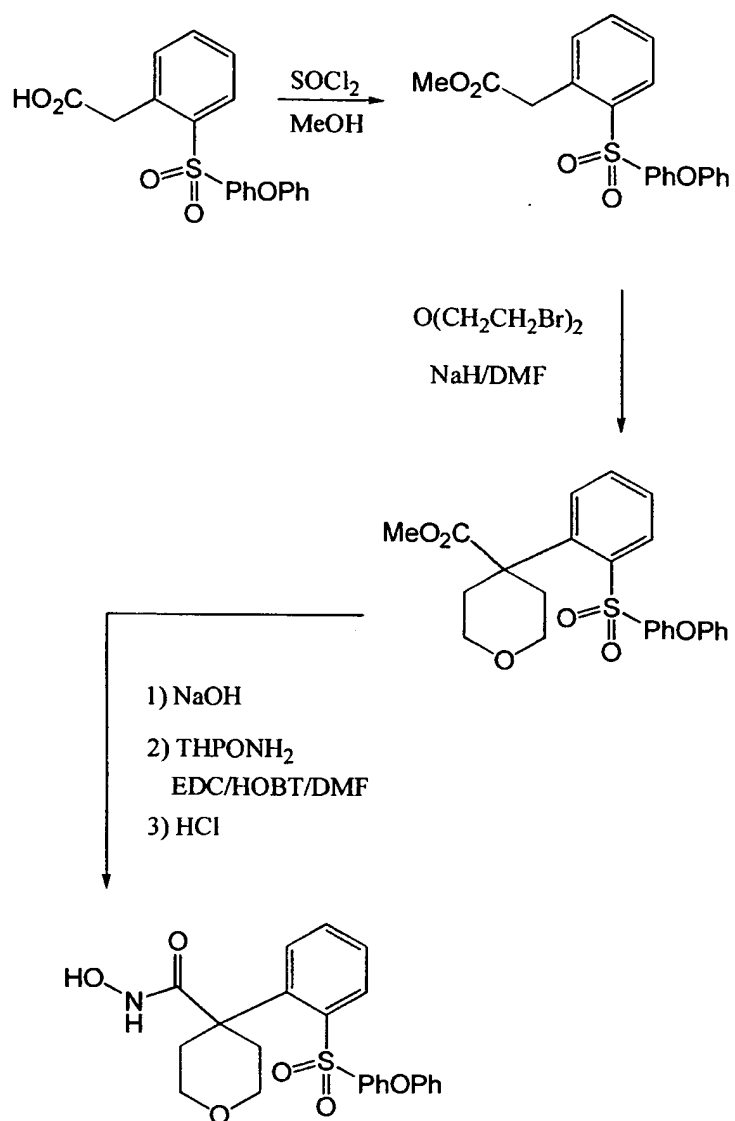
Example 1

Scheme 2



Example 2

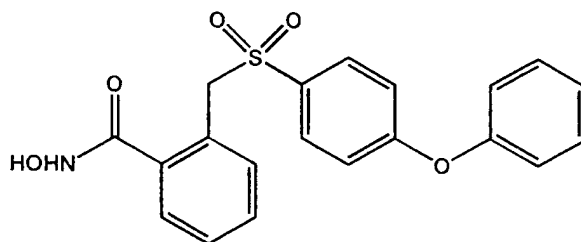
Scheme 3



Best Mode for Carrying Out the Invention

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its
5 fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limiting of the remainder of the disclosure in any way whatsoever.

- 10 Example 1: N-hydroxy-2-[[[4-phenoxyphenyl)-
sulfonyl]methyl]benzamide

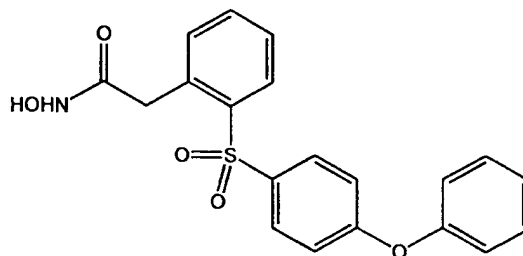


- 15 Part A: To a solution of phthalide (6.30 g, 47.0 mmol) in DMF (100 mL) was added K_2CO_3 (10.0 g, 49.4 mmol) and 4-(phenoxy)benzenethiol (9.59 g, 49.4 mmol) and the solution was heated to one hundred degrees Celsius for 2 hours. The solution was
20 diluted with H_2O and acidified with 1N HCl to pH = 1. The resulting tan solid was collected and washed with H_2O . The solid was dissolved into ethyl ether and dried over $MgSO_4$. Concentration *in vacuo* followed by recrystallization (ethyl ether/hexane) provided the
25 sulfide as a white solid (9.12 g, 58 %). MS(CI) MH^+ calculated for $C_{20}H_{16}O_3S$: 337, found 337. Analytical calculation for $C_{20}H_{16}O_3S$: C, 71.41; H, 4.79; S, 9.53. Found: C, 71.28; H, 4.67; S, 9.19.

Part B: To a solution of the sulfide of part A (3.00 g, 8.92 mmol) in dichloromethane (28 mL) and DMF (1 drop) was added oxalyl chloride (1.08 mL, 12.4 mmol) and the solution was stirred for 1 hour. After
5 concentration *in vacuo* the residue was dissolved into dichloromethane (16 mL) and the solution was cooled to zero degrees Celsius. Tetramethylsilyl hydroxylamine (2.55 mL, 20.8 mmol) was added and the solution was stirred for 1.5 hours. The solution was
10 diluted with dichloromethane and washed with 1N HCl, H₂O and saturated NaCl and dried over MgSO₄. Chromatography (on silica, ethyl acetate/hexane/toluene) provide the hydroxylamine as a clear paste (970 mg, 31%).

15 Part C: To a solution of the hydroxylamine of part B (970 mg, 2.76 mmol) in dichloromethane (25 mL) cooled to zero degrees Celsius was added 3-chloroperbenzoic acid (60%, 2.14 g, 7.45 mmol) and the solution was stirred for 3 hours at ambient
20 temperature. The solution was diluted with ethyl ether and washed with saturated Na₂SO₃, saturated NaHCO₃ and saturated NaCl and dried over MgSO₄. Reverse phase chromatography (on silica, acetonitrile/H₂O) provided the title compound as a
25 white solid (345 mg, 33%). MS(CI) MH⁺ calculated for C₂₀H₁₇NO₅S: 384, found 384. Analytical calculation for C₂₀H₁₇NO₅S•0.3H₂O: C, 61.70; H, 4.56; N, 3.60; S, 8.25. Found: C, 61.74; H, 4.42; N, 3.61; S, 8.31.

30 Example 2: N-hydroxy-2-[(4-phenoxyphenyl)-
sulfonyl]benzeneacetamide



Part A: To a solution of 4-(phenoxy)benzenethiol (6.06 g, 30.0 mmol) and K_2CO_3 (4.55 g, 33.0 mmol) in isopropanol (30 mL) was added 2-fluorobenzaldehyde (3.2 mL, 30.0 mmol). The solution was refluxed for 20 hours. The reaction was quenched by the addition of ice- H_2O and was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$. Filtration through a pad of silica gel provided the sulfide as a yellow solid (7.43 g, 81 %).

Part B: A solution of NaH (60 % dispersion in mineral oil, washed with hexane, 264 mg, 6.6 mmol) in THF (12 mL) was cooled to zero degrees Celsius and tetraethyl dimethylammoniummethylene diphosphonate (1.99 g, 6.0 mmol) was added. The solution was warmed to ambient temperature and the sulfide of part A (1.84 g, 6.0 mmol) was added. The solution was stirred for 4 hours at ambient temperature. The solution was extracted with ethyl acetate and washed with H_2O and dried over $MgSO_4$. Concentration *in vacuo* provided a brown oil which was dissolved in 6M HCl (10 mL) and the solution was heated to one hundred degrees Celsius for 1 hour. The solution was extracted with $CHCl_3$ and the organic layer was dried over $MgSO_4$. Concentration *in vacuo* provided the acid as an oil (918 mg, 48 %).

Part C: To a solution of the acid of part B (918 mg, 3 mmol) in acetic acid (30 mL) was added 30%

hydrogen peroxide (1.2 mL, 12 mmol) and the solution was heated to one hundred degrees Celsius for 40 minutes. The solution was lyophilized and chromatography (hexane/ethyl acetate) provided the sulfone as a foam (697 mg, 63 %).

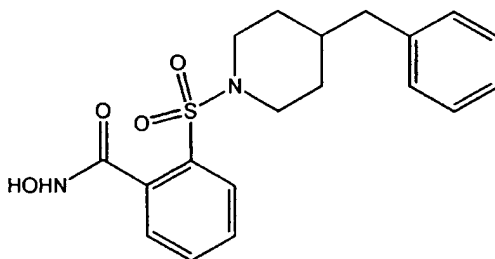
Part D: To a solution of the sulfone of part C (695 mg, 1.89 mmol) in acetonitrile (2 mL) was added tetrahydropyranyl hydroxylamine (270 mg, 2.3 mmol). After 5 minutes EDC (442 mg, 2.3 mmol) was added and the solution was stirred for 3 hours. The solution was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and H₂O. The organic layer was dried over MgSO₄. Chromatography (on silica gel, ethyl acetate/hexane) provided the ester as a white foam (688 mg, 77 %).

Part E: To a solution of the ester of part D (565 mg, 1.2 mmol) in methanol (10 mL) was added p-toluenesulfonic acid (25 mg) and the solution was stirred at ambient temperature for 2 hours. The solution was concentrated *in vacuo* and chromatography (chloroform/methanol) provided the title compound as a white solid (339 mg, 74 %).

Comparative Examples

25

Example 3: N-hydroxy-2-[[4-(phenylmethyl)-1-piperidinyl]sulfonyl]benzamide



Part A: To a solution of 2-chlorosulfonyl-benzoic acid ethyl ester, prepared per Nagasawa, et. al. J. Med. Chem. 1995, 38, 1865-1871, (5.80 g, 23.0 mmol) in acetonitrile (50 mL) was added 4-benzylpiperidine (4.38 mL, 25 mmol), triethylamine (3.78 mL, 27 mmol) and 4-dimethylaminopyridine (50 mg). The solution was stirred for 4 hours at ambient temperature and concentrated *in vacuo*. The residue was dissolved into 1N HCl and extracted with ethyl acetate. The organic layer was dried over MgSO₄ and filtered through a pad of silica gel to provide the sulfonamide as an oil (7.45 g, 84 %).

Part B: To a solution of the sulfonamide of part A (1.08 g, 2.80 mmol) in methanol (50 mL) and H₂O (20 mL) was added KOH (2 g) and the solution was stirred for 3 hours at ambient temperature. The solution was concentrated *in vacuo* and the remaining aqueous solution was acidified with 1N HCl. The solution was extracted with chloroform and the organic layer was dried over MgSO₄ and filtered through a pad of silica gel. Concentration *in vacuo* provided the acid as a white foam (996 mg, quantitative yield).

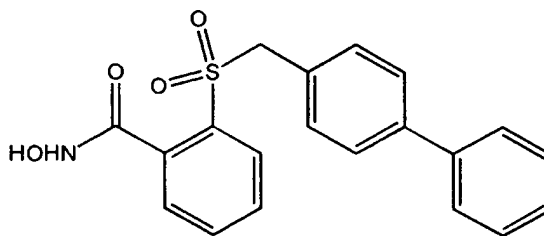
Part C: To a solution of the acid of part B (415 mg, 1.2 mmol) in acetonitrile (2 mL) was added tetrahydropyranyl hydroxylamine (200 mg, 1.7 mmol). After the solution was stirred for 5 minutes EDC (325 mg, 1.7 mmol) was added and the solution was stirred for 3 hours at ambient temperature. The solution was concentrated *in vacuo* and the residue was dissolved into H₂O and extracted with ethyl acetate. The organic layer was dried over MgSO₄. Chromatography

(on silica, ethyl acetate/hexane) provided the ester as a white solid (437 mg, 82 %).

Part D: To a solution of the ester of part C (437 mg, 0.98 mmol) in methanol (5 mL) was added p-toluenesulfonic acid (40 mg) and the solution was stirred for 1 hour at ambient temperature. The solution was concentrated *in vacuo*. Chromatography (ethyl acetate, 1% NH_4OH) provided the title compound as an oil (122 mg, 34 %).

10

Example 4: 2-[[[1,1'-biphenyl]-4-ylmethyl)-
sulfonyl]-N-hydroxybenzamide



15

Part A: To a solution of thiosalicylic acid (5.00 g, 32.4 mmol) and 4-phenylbenzyl chloride (6.57 g, 32.4 mmol) in ethanol (81 mL) and H_2O (40 mL) was added K_2CO_3 (4.48 g, 32.4 mmol) and the solution was heated to reflux for 2 hours. Upon cooling to ambient temperature a white solid formed. To this mixture is added 1N HCl (200 mL) and vacuum filtration provided the sulfide as a white solid (7.32 g, 70 %).

Part B: To a solution of the sulfide of part A (1.00 g, 3.12 mmol) in formic acid (17 mL) heated to fifty degrees Celsius was added 30% hydrogen peroxide (1.16 mL). The solution was stirred at fifty-five degrees Celsius for 3 hours followed by 40 hours at

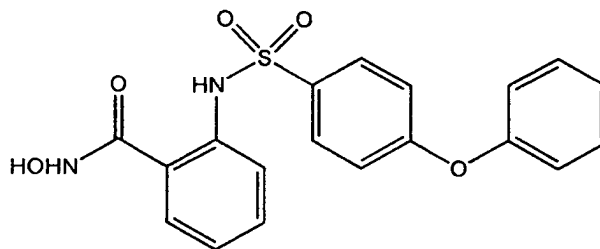
ambient temperature. The solution was concentrated and reverse phase chromatography (acetonitrile/H₂O) provided the sulfone as a white solid (500 mg, 45 %).

Part C: To a solution of the sulfone of part B (500 mg, 1.42 mmol) in DMF (2.8 mL) was added tetrahydropyranyl hydroxylamine (173 mg, 1.48 mmol), N-hydroxybenzotriazole (211 mg, 1.56 mmol) and EDC (299 mg, 1.56 mmol) and the solution was stirred for 18 hours at ambient temperature. The solution was concentrated *in vacuo* and the residue was dissolved into H₂O. The solution was extracted with ethyl acetate and the organic layer was washed with 1N HCl, saturated NaHCO₃, H₂O and saturated NaCl and dried over MgSO₄. Concentrated *in vacuo* provided the ester as a white solid (571 mg, 89 %). MS(CI) MH⁺ calculated for C₂₅H₂₅NO₅S: 452, found 452.

Part D: To a solution of the ester of part C (570 mg, 1.26 mmol) in methanol (10 mL) was added p-toluenesulfonic acid (15 mg) and the solution was stirred at ambient temperature for 1.5 hours. The solution was concentrated *in vacuo* and reverse phase chromatography (acetonitrile/H₂O) provided the title compound as a white solid (244 mg, 53 %). MS(EI) M⁺ calculated for C₂₀H₁₇NO₄S: 367, found 367. Analytical calculation for C₂₀H₁₇NO₄S: C, 65.38; H, 4.66; N, 3.81. Found: C, 65.01; H, 4.64; N, 4.04.

Example 5: N-hydroxy-2-[[[4-phenoxyphenyl)-
sulfonyllaminolbenzamide_____

30

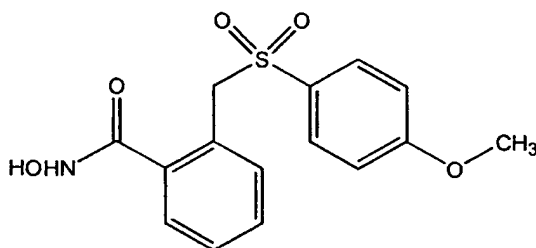


Part A: To a solution of isatoic anhydride (1.00 g, 6.13 mmol) in acetonitrile (3 mL) was added
5 tetrahydropyranyl hydroxylamine (1.56 g, 6.74 mmol) and the solution was heated to reflux for 2 hours. The solution was concentrated *in vacuo* and recrystallization of the residue (ethyl acetate/hexane) provided the ester as a white solid
10 (760 mg, 52 %). MS(CI) MH^+ calculated for $C_{12}H_{16}N_2O_3$: 237, found 237. Analytical calculation for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.82; H, 6.95; N, 11.76.

Part B: To a solution of 4-(phenoxy)benzene
15 sulfonyl chloride, prepared per J. Am. Chem. Soc., 1931, 93, 1112-1115) (341 mg, 1.27 mmol) in pyridine (2 mL) cooled to zero degrees Celsius was added the ester of part A (300 mg, 1.27 mmol) and the solution was stirred at zero degrees Celsius for 3 hours. The
20 solution was concentrated *in vacuo* and the residue was dissolved in 1N HCl and was extracted with ethyl acetate. The organic layer was washed with 1N HCl, H_2O and saturated NaCl and dried over $MgSO_4$. Chromatography (on silica gel, ethyl acetate/hexane)
25 provided the sulfone as a white solid (321 mg, 54%). MS(CI) MH^+ calculated for $C_{24}H_{24}N_2O_6S$: 469, found 469. Analytical calculation for $C_{24}H_{24}N_2O_6S$: C, 61.53; H, 5.16; N, 5.98; S, 6.84. Found: C, 61.10; H, 4.93; N, 5.86; S, 6.41.

Part C: Into a solution of the sulfone of part B (320 mg, 0.68 mmol) in methanol (3 mL) cooled to zero degrees Celsius was bubbled HCl gas for 5 minutes. The solution was concentrated *in vacuo* and the residue was triturated with ethyl ether. Collection by vacuum filtration provided the title compound as a pink solid (163 mg, 62 %). MS(CI) $\dot{M}H^+$ calculated for $C_{19}H_{16}N_2O_4S$: 385, found 385. Analytical calculation for $C_{19}H_{16}N_2O_6S \cdot 0.2H_2O$: C, 58.81; H, 4.26; N, 7.22; S, 8.26. Found: C, 58.88; H, 4.37; N, 6.98; S, 7.83.

Example 6 : N-hydroxy-2-[[[4-methoxyphenyl)-
sulfonyl]methyl]benzamide



Part A : A 500 mL round bottom flask equipped with magnetic stir bar and N_2 inlet was charged with 1.5 mL (1.7 g, 12.0 mM) 4-methoxybenzenethiol and 2.5 g (10.9 mM) methyl (2-bromomethyl)benzoate in acetone (100 mL). The solution was treated with 1.8 g (13.1 mM) potassium carbonate and heated at 55°C in an oil bath. The reaction mixture was stirred at 55°C for 17 hrs, then concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O , the layers were separated and the aqueous layer was extracted with EtOAc (1X), the organic phases were combined, washed

with 5% citric acid solution, saturated sodium bicarbonate solution and brine, dried (Na_2SO_4), and concentrated *in vacuo* to yield 3.3 g of product suitable for the next reaction.

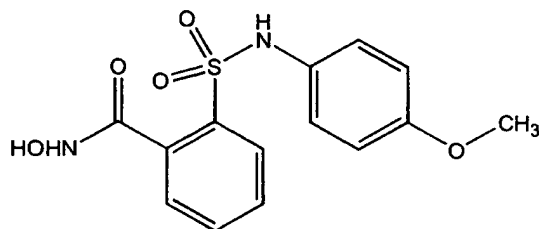
5 Part B : A 500 mL round bottom flask equipped with magnetic stir bar and N_2 inlet was charged with 3.1 g (10.8 mM) of product from Part A in 90 mL MeOH. The solution was then treated with 15 mL water and 13.9 g (22.6 mM) Oxone®. The reaction mixture was
10 stirred 17 hrs, then filtered. The filter cake was washed with MeOH, and the filtrate was concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O , the layers were separated and the aqueous layer was extracted with EtOAc (2X). The organic
15 phases were combined, washed with saturated sodium bicarbonate solution and brine, dried (MgSO_4), and concentrated *in vacuo* to yield the 3.3 g of crude product. This was chromatographed on silica gel using 25-45% ethyl acetate/hexane to yield 2.1 g of
20 pure product, $m/z = 321$ (M+H).

 Part C : A 250 mL round bottom flask equipped with magnetic stir bar and N_2 inlet was charged with 2.1 g (6.6 mM) of product from Part B in acetic acid (25 mL) and conc. HCl solution (25 mL) and the
25 solution was heated to reflux for a total of 24 hours. The reaction mixture was concentrated *in vacuo*, then two aliquots of toluene were added and stripped, then dried under high vacuum to yield 2.0 g of product suitable for the next reaction.

30 Part D : A 2-necked 50 mL round bottom flask equipped with addition funnel, thermometer, magnetic stir bar and N_2 inlet was charged with 1.0 mL of DMF in 10 mL CH_2Cl_2 . The solution was cooled in an ice

bath, then treated with 3.5 mL (0.9 g, 6.9 mM) of a 2.0 M oxalyl chloride solution in CH_2Cl_2 , then with a solution of 1.0 g (3.3 mM) of product from Part C in 5 mL DMF. The bath was removed and the reaction was stirred for 1 hour. This reaction mixture was added to a 2-necked 100 mL round-bottomed flask equipped with addition funnel, thermometer, magnetic stir bar and N_2 inlet and containing a cooled solution of 2.1 mL (1.1 g, 37.7 mM) of 50% aqueous hydroxylamine in THF (25 mL). The bath was then removed and the reaction mixture was stirred for 2 hours. The reaction was filtered, the filtrate was concentrated *in vacuo*, the residue was partitioned between EtOAc/water, the layers were separated, the aqueous layer was extracted with EtOAc (1X), the organic phases were combined and washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to yield 1.3 g of crude product. This was chromatographed on silica gel using 80% ethyl acetate/hexane to yield 0.5 g of pure product, $m/z = 328$ ($\text{M} + \text{Li}$).

Example 7 : N-hydroxy-2-[(4-methoxyanilino)-
sulfonylbenzamide

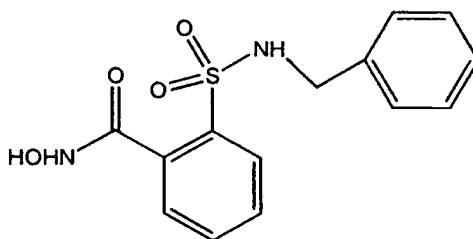


Part A : A 3-necked 100 mL round bottom flask equipped with addition funnel, thermometer, magnetic stir bar and N_2 inlet was charged with 0.5 g (4.3 mM)

of p-anisidine and 1.8 mL (1.3 g, 12.8 mM) triethylamine in CH_2Cl_2 (20 mL). The solution was cooled in an ice bath, then treated with a solution of 1.0 g (4.3 mM) methyl (2-chlorosulfonyl)benzoate in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 17 hrs, then concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O , the layers were separated and the organic phase was washed with 5% citric acid solution, saturated sodium bicarbonate solution and brine, dried (Na_2SO_4), and concentrated *in vacuo* to yield 0.9 g of crude product. This was chromatographed on silica gel using 20-30% ethyl acetate/hexane to yield 0.7 g of pure product, $m/z = 328$ (M+Li).

Part B : A 100 mL round bottom flask equipped with magnetic stir bar and N_2 inlet was charged with 0.7 g (2.1 mM) of the product from Part A and 0.7 g (10.2 mM) of hydroxylamine hydrochloride in 10 mL MeOH. The reaction was cooled to 0°C and charged with 0.4 g (16.4 mM) of sodium metal. After stirring for 17 hrs, the reaction was concentrated *in vacuo*, the residue was slurried in 20 mL of water, then acidified using 2N HCl solution. The aqueous slurry was extracted with EtOAc (3X). The organic layers were combined and washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to yield 0.6 g of crude product. The addition of methylene chloride to the crude product precipitated an off-white solid. Filtration gave 0.2 g of pure product, $m/z = 323$ (M+Li).

Example 8 : N-hydroxy-2-[(benzylamino)-
sulfonyl]benzamide



Part A : A 3-necked 100 mL round bottom flask equipped with addition funnel, thermometer, magnetic stir bar and N₂ inlet was charged with 0.5 mL (0.5 g, 4.3 mM) of benzylamine and 1.8 mL (1.3 g, 12.8 mM) triethylamine in CH₂Cl₂ (20 mL). The solution was cooled in an ice bath, then treated with a solution of 1.0 g (4.3 mM) methyl (2-chlorosulfonyl)benzoate in CH₂Cl₂ (10 mL). The reaction mixture was stirred for 2 hrs, then concentrated *in vacuo*. The residue was partitioned between EtOAc and H₂O, the layers were separated and the organic phase was washed with 5% citric acid solution, saturated sodium bicarbonate solution and brine, dried (Na₂SO₄), and concentrated *in vacuo* to yield 0.9 g of crude product. This was chromatographed on silica gel using 20% ethyl acetate/hexane to yield 0.7 g of pure product, m/z= 312 (M+Li).

Part B : A 100 mL round bottom flask equipped with magnetic stir bar and N₂ inlet was charged with 0.7 g (2.1 mM) of the product from Part A and 0.7 g (10.6 mM) of hydroxylamine hydrochloride in 10 mL MeOH. The reaction was cooled to 0°C and charged with 0.4 g (17.0 mM) of sodium metal. After stirring for 17 hrs, the reaction was concentrated *in vacuo*, the residue was slurried in 20 mL of water, then acidified using 2N HCl solution. The aqueous slurry

was extracted with EtOAc (3X). The organic layers were combined and washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to yield 0.3 g of crude product. The addition of methylene chloride to the
5 crude product precipitated a white solid. Filtration gave 0.1 g of pure product, $m/z = 307$ (M+H).

Example 9: In Vitro Metalloprotease Inhibition

The compounds prepared in the manner
10 described in Examples 1 to 9 were assayed for activity by an *in vitro* assay. Following the procedures of Knight et al., *FEBS Lett.* 296(3):263 (1992). Briefly, 4-aminophenylmercuric acetate (APMA) or trypsin activated MMPs were incubated with
15 various concentrations of the inhibitor compound at room temperature for 5 minutes.

More specifically, recombinant human MMP-13 and MMP-1 enzymes were prepared in laboratories of the assignee. MMP-13 was expressed in baculovirus as
20 a proenzyme, and purified first over a heparin agarose column and then over a chelating zinc chloride column. The proenzyme was activated by APMA for use in the assay. MMP-1 expressed in transfected HT-1080 cells was provided by Dr. Howard Welgus of
25 Washington University, St. Louis, MO. The enzyme was also activated using APMA and was then purified over a hydroxamic acid column.

The enzyme substrate is a methoxycoumarin-containing polypeptide having the following sequence:

30 MCA-ProLeuGlyLeuDpaAlaArgNH₂, wherein MCA is methoxycoumarin and Dpa is 3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl alanine. This substrate is

commercially available from Baychem as product
M-1895.

The buffer used for assays contained 100 mM
Tris-HCl, 100 mM NaCl, 10 mM CaCl₂ and 0.05 percent
5 polyethyleneglycol (23) lauryl ether at a pH value of
7.5. Assays were carried out at room temperature,
and dimethyl sulfoxide (DMSO) at a final
concentration of 1 percent was used to dissolve
inhibitor compound.

10 The assayed inhibitor compound in
DMSO/buffer solution was compared to an equal amount
of DMSO/buffer with no inhibitor as control using
Microfluor™ White Plates (Dynatech). The inhibitor
or control solution was maintained in the plate for
15 10 minutes and the substrate was added to provide a
final concentration of 4 μM.

In the absence of inhibitor activity, a
fluorogenic peptide was cleaved at the gly-leu
peptide bond, separating the highly fluorogenic
20 peptide from a 2,4-dinitrophenyl quencher, resulting
in an increase of fluorescence intensity (excitation
at 328 nm/emission at 415 nm). Inhibition was
measured as a reduction in fluorescent intensity as a
function of inhibitor concentration, using a Perkin
25 Elmer L550 plate reader. The IC₅₀ values were
calculated from those values. The results are set
forth in the Inhibition Table (Table 38) below,
reported in terms of IC₅₀ to three significant
figures.

30

Inhibition Table 38

(IC₅₀ values in nM)

<u>Example</u>	<u>MMP -13</u>	<u>MMP-1</u>	<u>MMP-2</u>
1	45	>10,000	10
2	2	900	0.3
3	1000	>10,000	148
4	>10,000	>10,000	>10,000
5	>10,000	>10,000	3500
6	4000	>10,000	--
7	>10,000	>10,000	--
8	>10,000	>10,000	--

5

Example 10: In Vivo Angiogenesis Assay

The study of angiogenesis depends on a
 10 reliable and reproducible model for the stimulation
 and inhibition of a neovascular response. The
 corneal micropocket assay provides such a model of
 angiogenesis in the cornea of a mouse. See, *A Model
 of Angiogenesis in the Mouse Cornea*; Kenyon, BM,
 15 et al., *Investigative Ophthalmology & Visual Science*,
 July 1996, Vol. 37, No. 8.

In this assay, uniformly sized Hydron™
 pellets containing bFGF and sucralfate are prepared
 and surgically implanted into the stroma mouse cornea
 20 adjacent to the temporal limbus. The pellets are
 formed by making a suspension of 20 µL sterile saline
 containing 10 µg recombinant bFGF, 10 mg of
 sucralfate and 10 µL of 12 percent Hydron™ in
 ethanol. The slurry is then deposited on a 10 x 10 mm

///

piece of sterile nylon mesh. After drying, the nylon fibers of the mesh are separated to release the pellets.

The corneal pocket is made by anesthetizing a 7 week old C57Bl/6 female mouse, then proptosing the eye with a jeweler's forceps. Using a dissecting microscope, a central, intrastromal linear keratotomy of approximately 0.6 mm in length is performed with a #15 surgical blade, parallel to the insertion of the lateral rectus muscle. Using a modified cataract knife, a lamellar micropocket is dissected toward the temporal limbus. The pocket is extended to within 1.0 mm of the temporal limbus. A single pellet is placed on the corneal surface at the base of the pocket with a jeweler's forceps. The pellet is then advanced to the temporal end of the pocket. Antibiotic ointment is then applied to the eye.

Mice are dosed on a daily basis for the duration of the assay. Dosing of the animals is based on bioavailability and overall potency of the compound. an exemplary dose is 50 mg/kg bid, po. Neovascularization of the corneal stroma begins at about day three and is permitted to continue under the influence of the assayed compound until day five. At day five, the degree of angiogenic inhibition is scored by viewing the neovascular progression with a slit lamp microscope.

The mice are anesthetized and the studied eye is once again proptosed. The maximum vessel length of neovascularization, extending from the limbal vascular plexus toward the pellet is measured. In addition, the contiguous circumferential zone of neovascularization is measured as clock hours, where

30 degrees of arc equals one clock hour. The area of angiogenesis is calculated as follows.

$$\text{area} = \frac{(0.4 \times \text{clock hours} \times 3.14 \times \text{vessel length (in mm)})}{2}$$

5

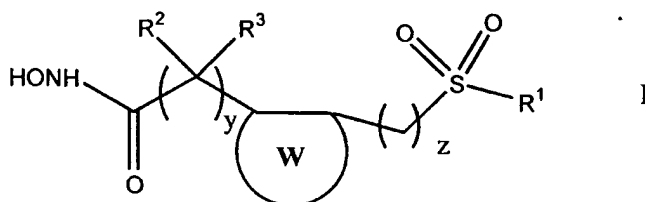
The studied mice are thereafter compared to control mice and the difference in the area of neovascularization is recorded. A contemplated compound typically exhibits about 25 to about 75 percent inhibition, whereas the vehicle control exhibits zero percent inhibition.

From the foregoing, it will be observed that numerous modifications and variations can be effectuated without departing from the true spirit and scope of the novel concepts of the present invention. It is to be understood that no limitation with respect to the specific example presented is intended or should be inferred. The disclosure is intended to cover by the appended claims all such modifications as fall within the scope of the claims.

WHAT IS CLAIMED IS:

1. A compound corresponding to Formula I:

5



wherein

y and z are each zero or one and the sum of
10 z+y is one;

the ring structure W is a 5- or 6-membered
divalent aromatic or heteroaromatic ring;

R¹ is a substituent containing a 5- or 6-
membered cyclohydrocarbyl, heterocyclo, aryl or
15 heteroaryl radical bonded directly to the depicted
SO₂-group and having a length greater than about that
of a hexyl group and less than about that of an
eicosyl group, said R¹ defining a three-dimensional
volume, when rotated about an axis drawn through the
20 SO₂-bonded 1-position and the 4-position of a 6-
membered ring radical or drawn through the SO₂-bonded
1-position and the center of 3,4-bond of a 5-membered
ring radical, whose widest dimension in a direction
transverse to the axis of rotation is about that of
25 one furanyl ring to about that of two phenyl rings;
and

R^2 and R^3 are independently hydrido, C_1-C_4 hydrocarbyl, hydroxyl or amino, or R^2 and R^3 together with the depicted carbon atom to which they are bonded form a 6-membered heterocyclic ring in which
5 the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally substituted with one or two oxygens when sulfur and being optionally substituted with a moiety selected from the group consisting of a C_1-C_4 hydrocarbyl, C_3-C_6
10 cyclohydrocarbyl, C_1-C_4 acylhydrocarbyl, and sulfonyl C_1-C_4 hydrocarbyl group when nitrogen.

2. The compound according to claim 1 wherein said 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical of R^1 is
15 substituted with a substituent, R^4 , that has a chain length of 3 to about 14 carbon atoms.

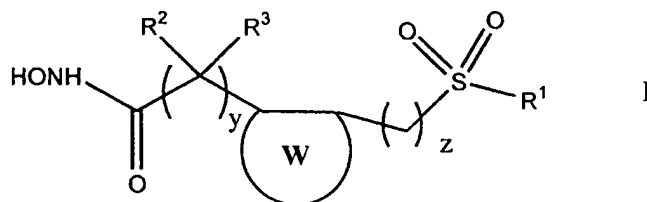
3. The compound according to claim 2
20 wherein said R^4 substituent is selected from the group consisting of a phenyl group, a phenoxy group, a thiophenoxy group, an anilino group, a phenylazo group, a phenylureido, a benzamido, a nicotinamido, an isonicotinamido, a picolinamido group, a
25 heterocyclo, heterocyclohydrocarbyl, arylheterocyclohydrocarbyl, arylhydrocarbyl, heteroarylhydrocarbyl, heteroarylheterocyclohydrocarbyl, arylhydrocarbyloxyhydrocarbyl, aryloxyhydrocarbyl,
30 hydrocarboylhydrocarbyl, arylhydrocarboylhydrocarbyl, arylcarbonylhydrocarbyl, arylazoaryl, arylhydrazinoaryl, hydrocarbylthiohydrocarbyl,

hydrocarbylthioaryl, arylthiohydrocarbyl,
heteroarylthiohydrocarbyl,
hydrocarbylthioarylhydrocarbyl,
arylhydrocarbylthiohydrocarbyl,
5 arylhydrocarbylthioaryl, arylhydrocarbylamino,
heteroarylhydrocarbylamino, and a heteroarylthio
group.

4. The compound according to claim 3
10 wherein said R⁴ substituent is itself substituted by
one or more substituents selected from the group
consisting of a halogen, hydrocarbyl, hydrocarbyloxy,
nitro, cyano, perfluorohydrocarbyl,
trifluoromethylhydrocarbyl, hydroxy, mercapto,
15 hydroxycarbonyl, aryloxy, arylthio, arylamino,
arylhydrocarbyl, aryl, heteroaryloxy, heteroarylthio,
heteroarylamino, heteroarhydrocarbyl,
hydrocarbyloxycarbonylhydrocarbyl, heterocyclooxy,
hydroxycarbonylhydrocarbyl, heterocyclothio,
20 heterocycloamino, cyclohydrocarbyloxy,
cyclohydrocarbylthio, cyclohydrocarbylamino,
heteroarylhydrocarbyloxy, heteroarylhydrocarbylthio,
heteroarylhydrocarbylamino, arylhydrocarbyloxy,
arylhydrocarbylthio, arylhydrocarbylamino,
25 heterocyclic, heteroaryl, hydroxycarbonyl-
hydrocarbyloxy, alkoxycarbonylalkoxy, hydrocarbyloyl,
arylcarbonyl, arylhydrocarbyloyl, hydrocarbyloxy,
arylhydrocarbyloxy, hydroxyhydrocarbyl,
hydroxyhydrocarbyloxy, hydrocarbylthio,
30 hydrocarbyloxyhydrocarbylthio,
hydrocarbyloxycarbonyl,
hydroxycarbonylhydrocarbyloxy, hydrocarbyloxy-
carbonylhydrocarbyl, hydrocarbylhydroxycarbonyl-

- hydrocarbylthio,
hydrocarbyloxycarbonylhydrocarbyloxy,
hydrocarbyloxycarbonylhydrocarbylthio, amino,
hydrocarbylcarbonylamino, arylcarbonylamino,
5 cyclohydrocarbylcarbonylamino,
heterocyclohydrocarbylcarbonylamino,
arylhydrocarbylcarbonylamino,
heteroarylcarbonylamino,
heteroarylhydrocarbylcarbonylamino,
10 heterocyclohydrocarbyloxy, hydrocarbylsulfonylamino,
arylsulfonylamino, arylhydrocarbylsulfonylamino,
heteroarylsulfonylamino, heteroarylhydrocarbyl-
sulfonylamino, cyclohydrocarbylsulfonylamino,
heterocyclohydrocarbylsulfonylamino and N-
15 monosubstituted or N,N-disubstituted aminohydrocarbyl
group, wherein the substituent(s) on the nitrogen are
selected from the group consisting of hydrocarbyl,
aryl, arylhydrocarbyl, cyclohydrocarbyl,
arylhydrocarbyloxycarbonyl, hydrocarbyloxycarbonyl,
20 and hydrocarbonyl, or wherein the nitrogen and two
substituents attached thereto form a 5- to 8-membered
heterocyclic or heteroaryl ring group.

- 25 5. A compound corresponding to Formula I:



wherein

y and z are each zero or one and the sum of z+y is one;

the ring structure W is a 5- or 6-membered divalent aromatic or heteroaromatic ring;

5 R¹ is a substituent containing a 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical bonded directly to the depicted SO₂-group that is itself substituted at its own 4-
10 position when a 6-membered ring and at its own 3- or 4-position when a 5-membered ring with a substituent R⁴ selected from the group consisting of one other single-ringed cyclohydrocarbyl, heterocyclo, aryl or heteroaryl group, a C₃-C₁₄ hydrocarbyl group, a C₂-C₁₄ hydrocarbyloxy group, a phenoxy group, a
15 thiophenoxy group, a 4-thiopyridyl group, a phenylazo group, a phenylureido group, a nicotinamido group, an isonicotinamido group, a picolinamido group, an anilino group and a benzamido group; and

 R² and R³ are independently hydrido, C₁-C₄
20 hydrocarbyl, hydroxyl or amino, or R² and R³ together with the depicted carbon atom to which they are bonded form a 6-membered heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally substituted with one or
25 two oxygens when sulfur and being optionally substituted with a moiety selected from the group consisting of a C₁-C₄ hydrocarbyl, C₃-C₆ cyclohydrocarbyl, C₁-C₄ acylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl group when nitrogen.

30

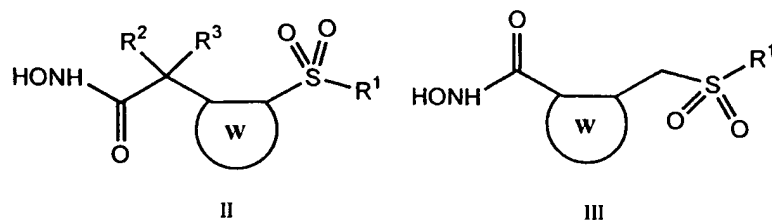
6. The compound according to claim 5 wherein said R^1 substituent is PhR^4 in which Ph is phenyl substituted with R^4 at the 4-position, and said R^4 is a phenyl, phenoxy, thiophenoxy, phenylazo, benzamido, anilino, nicotinamido, isonicotinamido, picolinamido or phenylureido group that is optionally substituted at the meta- or para-position or both with a moiety that is selected from the group consisting of a halogen, a C_1 - C_9 hydrocarbyloxy group, a C_1 - C_{10} hydrocarbyl group, a di- C_1 - C_9 hydrocarbylamino group, a carboxyl C_1 - C_8 hydrocarbyl group, a C_1 - C_4 hydrocarbyloxy carbonyl C_1 - C_4 hydrocarbyl group, a C_1 - C_4 hydrocarbyloxycarbonyl C_1 - C_4 hydrocarbyl group and a carboxamido C_1 - C_8 hydrocarbyl group, or is substituted at the meta- and para-positions by two methyl groups or by a methylenedioxy group.

7. The compound according to claim 5 wherein z is one and y is zero.

8. The compound according to claim 5 wherein y is one and z is zero.

9. The compound according to claim 5 wherein said R^1 substituent has a length greater than that of an octyl group and less than that of a stearyl group.

10. A compound corresponding to Formulas II or III:



wherein

the ring structure W is a 5- or 6-membered divalent aromatic or heteroaromatic;

R¹ is a substituent containing a single cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical bonded directly to the depicted SO₂-group that is itself substituted at its own 4-position when a 6-membered ring and at its own 3- or 4-position when a 5-membered ring with a substituent R⁴ selected from the group consisting of one other single-ringed aryl or heteroaryl group, a C₃-C₁₄ hydrocarbyl group, a C₂-C₁₄ hydrocarbyloxy group, a phenoxy group, a thiophenoxy group, a 4-thiopyridyl group, a phenylazo group, a phenylureido group, a nicotinamido group, an isonicotinamido group, a picolinamido group, an anilino group and a benzamido group;

R² and R³ are independently hydrido, C₁-C₄ hydrocarbyl, hydroxyl or amino, or R² and R³ together with the depicted carbon atom to which they are bonded form a 6-membered heterocyclic ring in which the heteroatom is oxygen, sulfur or nitrogen, said heteroatom being optionally substituted with one or two oxygens when sulfur and being optionally substituted with a moiety selected from the group consisting of a C₁-C₄ hydrocarbyl, C₃-C₆

cyclohydrocarbyl, C₁-C₄ acylhydrocarbyl, and sulfonyl C₁-C₄ hydrocarbyl group when nitrogen.

11. The compound according to claim 10
5 wherein said R⁴ is a phenyl, phenoxy, anilino, thiophenoxy, benzamido, nicotinamido, isonicotinamido, picolinamido or phenylureido group that is itself optionally substituted at meta or para position or both with a moiety that is selected from
10 the group consisting of a halogen, a C₁-C₉ hydrocarbyloxy group, a C₁-C₁₀ hydrocarbyl group, a di-C₁-C₉ hydrocarbylamino group, a carboxyl C₁-C₈ hydrocarbyl group, a C₁-C₄ hydrocarbyloxy carbonyl C₁-C₄ hydrocarbyl group, a C₁-C₄
15 hydrocarbyloxycarbonyl C₁-C₄ hydrocarbyl group, and a carboxamido C₁-C₈ hydrocarbyl group, or is substituted at the meta- and para-positions by two methyl groups or by a C₁-C₂ alkylenedioxy group.

20 12. The compound according to claim 11 wherein said R⁴ is a phenoxy or thiophenoxy group that is unsubstituted.

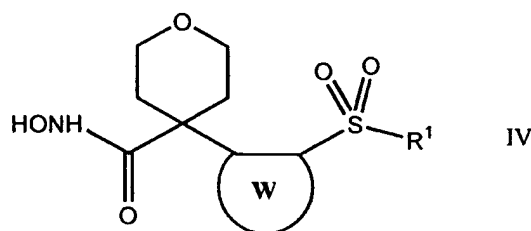
13. The compound according to claim 10
25 that corresponds in structure to Formula II.

14. The compound according to claim 10 that corresponds in structure to Formula III.

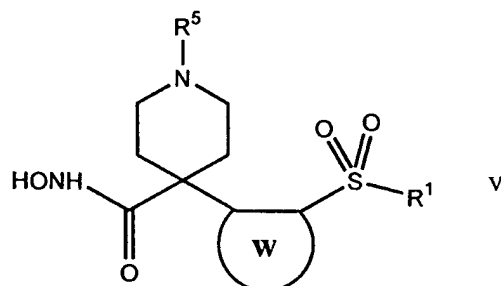
30 15. The compound according to claim 10 wherein R² and R³ together with the carbon atom to

which they are bonded form a 4-tetrahydropyranyl or 4-piperidinyl group, said 4-piperidinyl group when present being optionally substituted with a moiety R^5 selected from the group consisting of a C_1 - C_4 hydrocarbyl, C_3 - C_6 cyclohydrocarbyl, C_1 - C_4 acylhydrocarbyl, and sulfonyl C_1 - C_4 hydrocarbyl group.

16. The compound according to claim 15 corresponding in structure to Formula IV



17. The compound according to claim 15 corresponding in structure to Formula V



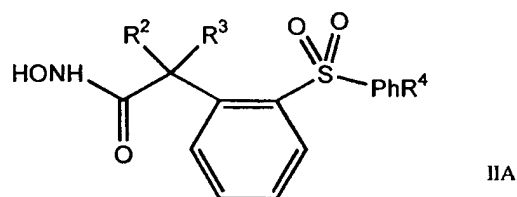
wherein R^5 is selected from the group consisting of a C_1 - C_4 hydrocarbyl, C_3 - C_6 cyclohydrocarbyl, C_1 - C_4 acylhydrocarbyl, and a sulfonyl C_1 - C_4 hydrocarbyl group

18. The compound according to claim 10 wherein said 5- or 6-membered divalent aromatic or

heteroaromatic ring W is selected from the group consisting of a 1,2-phenylene, 2,3-pyridinylene, 3,4-pyridinylene, 4,5-pyridinylene, 2,3-pyrazinylene, 4,5-pyrimidinylene, and 5,6-pyrimidinylene group.

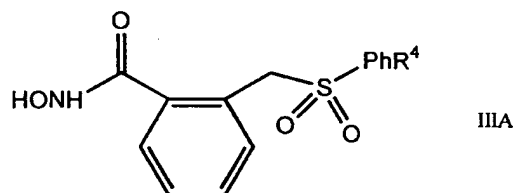
5

19. The compound according to claim 10 corresponding in structure to Formula IIA



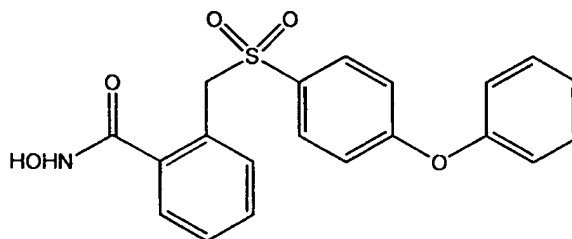
10

20. The compound according to claim 10 corresponding in structure to Formula IIIA



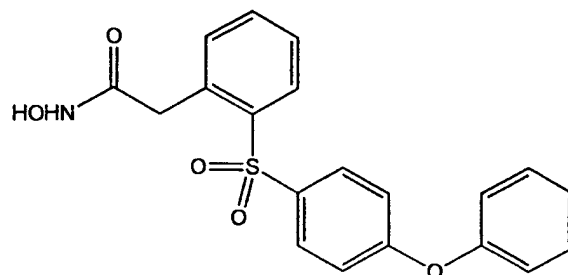
15

21. A compound corresponding to the formula

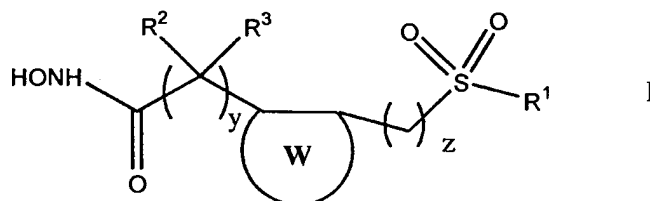


20

22. A compound corresponding to the formula



23. A process for treating a host mammal having a condition associated with pathological matrix metalloprotease activity that comprises administering a compound corresponding in structure to Formula I in an MMP enzyme-inhibiting effective amount to a mammalian host having such a condition:



10

wherein

y and z are each zero or one and the sum of z+y is one;

15

the ring structure W is a 5- or 6-membered divalent aromatic or heteroaromatic ring;

R¹ is a substituent containing a 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl or heteroaryl radical bonded directly to the depicted SO₂-group and having a length greater than about that of a hexyl group and less than about that of an eicosyl group, said R¹ defining a three-dimensional volume, when rotated about an axis drawn through the SO₂-bonded 1-position and the 4-position of a 6-

25

membered ring radical or drawn through the SO₂-bonded
1-position and the center of 3,4-bond of a 5-membered
ring radical, whose widest dimension in a direction
transverse to the axis of rotation is about that of
5 one furanyl ring to about that of two phenyl rings;
R² and R³ are independently hydrido, C₁-C₄
hydrocarbyl, hydroxyl or amino, or R² and R³ together
with the depicted carbon atom to which they are
bonded form a 6-membered heterocyclic ring in which
10 the heteroatom is oxygen, sulfur or nitrogen, said
heteroatom being optionally substituted with one or
two oxygens when sulfur and being optionally
substituted with a moiety selected from the group
consisting of a C₁-C₄ hydrocarbyl, C₃-C₆
15 cyclohydrocarbyl, C₁-C₄ acylhydrocarbyl, and a
sulfonyl C₁-C₄ hydrocarbyl group when nitrogen.

24. The process according to claim 21
wherein R¹ is a single-ringed cyclohydrocarbyl,
20 heterocyclo, aryl or heteroaryl substituent that is
5- or 6-membered, and is itself substituted at its
own 4-position when a 6-membered ring and at its own
3- or 4-position when a 5-membered ring with a
substituent R⁴ selected from the group consisting of
25 one other single-ringed aryl or heteroaryl group, a
C₃-C₁₄ hydrocarbyl group, a C₂-C₁₄ hydrocarbyloxy
group, a phenoxy group, a thiophenoxy group, an
anilino group, a 4-thiopyridyl group, a phenylazo
group, a phenylureido group, a nicotinamido group, an
30 isonicotinamido group, a picolinamido group and a
benzamido group.

25. The process according to claim 21 wherein said R¹ substituent is PhR⁴ in which Ph is phenyl substituted with R⁴ at the 4-position, and R⁴ is a phenyl, phenoxy, anilino, thiophenoxy, phenylazo, benzamido, nicotinamido, isonicotinamido, picolinamido or phenylureido group

26. The process according to claim 21 wherein said R¹ substituent is PhR⁴ in which Ph is phenyl substituted with R⁴ at the 4-position, and said R⁴ is a phenyl, phenoxy, anilino, thiophenoxy, phenylazo, benzamido, nicotinamido, isonicotinamido, picolinamido or phenylureido group that is substituted at the meta- or para-position or both with a moiety that is selected from the group consisting of a halogen, a C₁-C₉ hydrocarbyloxy group, a C₁-C₁₀ hydrocarbyl group, a di-C₁-C₉ hydrocarbylamino group, a carboxyl C₁-C₈ hydrocarbyl group, a C₁-C₄ hydrocarbyloxy carbonyl C₁-C₄ hydrocarbyl group, a C₁-C₄ hydrocarbyloxycarbonyl C₁-C₄ hydrocarbyl group and a carboxamido C₁-C₈ hydrocarbyl group, or is substituted at the meta- and para-positions by two methyl groups or by a methylenedioxy group.

25

27. The process according to claim 21 wherein said R¹ substituent has a length greater than that of an octyl group and less than that of a stearyl group.

30

28. The process according to claim 21 wherein said R³ is a phenoxy or thiophenoxy group that is unsubstituted.

5 29. The process according to claim 21 wherein said compound is administered a plurality of times.